IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

BIO-TECHNOLOGY GENERAL CORP.,	)	
Plaintiff,	)	
v.	)	Civ. No. 02-235-SLR
NOVO NORDISK A/S and NOVO NORDISK PHARMACEUTICALS, INC.,	)	
Defendants.	)	

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OPINION

Wilmington, Delaware
Dated: August 3, 2004

ROBINSON, Chief Judge

I. INTRODUCTION

Plaintiff Bio-Technology General Corp. ("BTG") appeals the decision of the Board of Patent Appeals and Interferences (the "Board") of the United States Patent and Trademark Office ("PTO") in Blumberg v. Dalboge, Interference No. 104,422, pursuant to 35 U.S.C. § 146. The Board granted the benefit of priority of invention for the subject matter of the interference count generally directed to ripe human growth hormone ("ripe hGH") to defendants Novo Nordisk A/S and Novo Nordisk Pharmaceuticals, Inc. (collectively, "Novo"). As a result of this priority award, Novo maintained its United States Patent No. 5,633,352 (the "'352 patent") and BTG was denied entitlement to a patent based upon its United States Application No. 09/023,248 (the "'248 application"). The court has jurisdiction over this suit pursuant to 28 U.S.C. §§ 1331, 1338. The following are the court's findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

II. FINDINGS OF FACT

A. The Parties

1. BTG is a corporation organized under the laws of the State of Delaware with its principal place of business in Iselin, New Jersey. (D.I. 1 at ¶ 3)

2. Novo Nordisk A/S is a corporation organized under the laws of the Kingdom of Denmark with its principal place of

business in Bagsvaerd, Denmark. (D.I. 1 at ¶ 4; D.I. 7 at ¶ 4)

3. Novo Nordisk Pharmaceuticals, Inc. is a corporation organized under the laws of the State of Delaware with its principal place of business in Princeton, New Jersey. (D.I. 1 at ¶ 5; D.I. 7 at ¶ 5)

B. The Technology in General

4. Proteins and peptides consist of chains of amino acids. (BTX 3 at 4) The amino acids are selected from the group of about twenty naturally occurring cellular amino acids. (Id.) The left-hand end of the amino acid chain is referred to as the N-terminus, and the right-hand end of the chain is referred to as the C-terminus.

5. Genes are comprised of long chains of DNA, which consist of nucleotide triplets. (Id.) These nucleotide triplets are referred to as codons. (Id.) When a particular protein is to be synthesized, messenger RNA ("mRNA") copy the region of the DNA that codes for the protein (i.e., the codons specific to the protein). (Id.) The mRNA are then used by the cell as a pattern to produce the protein. (Id.)

6. A cell seldomly synthesizes a desired protein directly. (Id. at 5) Rather, the first product, commonly referred to as a "fusion protein," typically consists of the final protein plus a pro-sequence. (Id.) The pro-sequence consists of additional amino acids attached to the N-terminus of the final desired protein. (Id.) To obtain the final desired

protein, proteolytic enzymes cleave the peptide bonds between the pro-sequence and the final desired protein. (Id. at 7)

7. Two types of proteolytic enzymes may be employed in protein synthesis: (1) exoproteases; and (2) endoproteases. Exoproteases cleave amino acids from the end of a protein chain at either the N-terminus or the C-terminus. Endoproteases, in contrast, cleave amino acids in the interior of a protein chain.

8. Aminopeptidases are exoproteases and cleave amino acids from the N-terminus of a protein chain. *Aeromonas*, Aminopeptidase I ("AP I"), leucine aminopeptidase ("LAP"), and dipeptidyl aminopeptidase I ("DAP I") are four distinct aminopeptidases.

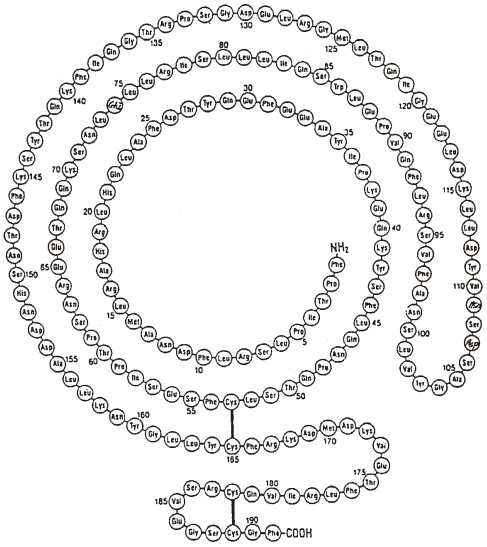
9. LAP has the enzyme classification number E.C. 3.4.11.1. It releases amino acids sequentially one-by-one from the N-terminus of a peptide by hydrolizing the amide bonds found in the peptide. (BTX 319) LAP is known to have an optimal pH in the range of 7.5-9.0 and is unstable in the region of 4 to 5. (BTX 23; BTX 318) If the peptide to be cleaved by LAP contains a proline residue, LAP will not cleave the amino acid that precedes the proline residue because LAP is unable to hydrolize the bond that exists between the proline residue and the preceding amino acid. (DTX 319 at 433)

10. DAP I has the enzyme classification number E.C. 3.4.14.1 and is also referred to as cathepsin C. It releases amino acids sequentially in dipeptidyl units from the N-terminus

of a peptide. It is known to have an optimum pH in the range of 4 to 6. (BTX 23)

C. Human Growth Hormone

11. Human growth hormone ("hGH") is a specific protein consisting of 191 amino acids. It is naturally secreted by the pituitary gland. (Paper 124 at 2) Proline is the second to last amino acid located at the N-terminus. The amino acid sequence for hGH is shown in the figure below.



12. Human growth hormone is administered to treat conditions such as dwarfism, infertility, wound care, and intoxication. (BTX 36 at NNG0025821)

13. Pituitary-derived hGH may contain contaminants that cause a variety of diseases such as Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, and Kuru. ('352 patent, col. 3 at ll. 42-46) The risk of these diseases

has lead some countries to ban the use of pituitary-derived hGH. (BTX 36 at NNG0025821) For this reason, the need arose to produce hGH synthetically using recombinant DNA technology.

14. There are two basic approaches to make hGH using recombinant DNA technology: (1) an enzymatic cleavage system; and (2) a secretion system.

a. Enzymatic Cleavage System

15. In this approach, the gene for hGH is transferred to a host organism, such as the *E. coli* bacteria. The *E. coli* bacteria are transformed to express the fusion protein consisting of hGH with pro-sequence attached to the N-terminus. ('352 patent, col. 3 at ll. 26-29) The pro-sequence is cleaved from the fusion protein using an exopeptidase to form biosynthetic hGH. The following scheme shows this enzymatic cleavage system:

$$A - hGH \xrightarrow{\text{enzyme}} hGH$$

where A is a pro-sequence. (BTX 23)

16. If LAP is selected as the cleavage enzyme, cleavage terminates at the amino acid preceding proline, as noted above, leaving hGH as the final product. (Id.) The concept of using proline in conjunction with LAP to control the recombinant DNA synthesis of hGH is referred to as the "Y-pro stop signal strategy."

b. Secretion System

17. In this approach, host organisms such as yeast

are transformed so that they express a pre-protein consisting of the desired protein with a leader or signal sequence attached to the N-terminus. The pre-protein is transported through the cell membrane. During transport, an endopeptidase, referred to as a "signal peptidase," clips off the leader sequence. The desired protein then is secreted outside the cell.

18. Human growth hormone is expressed in the human pituitary gland as a pre-protein having a 26-amino acid leader sequence. The pre-hGH is transported through the cell membrane where the 26-amino acid leader sequence is clipped off. The desired 191-amino acid hGH then is secreted outside the human pituitary gland.

D. Novo's '352 Patent

19. The '352 patent, entitled "Biosynthetic Human Growth Hormone," was filed on March 10, 1995.

20. The '352 patent was granted on May 27, 1997.

21. The named inventors include Henrik Dalboge, John Pedersen, Thorkild Christensen, Jorli W. Ringsted, and Torben E. Jessen.

22. The '352 patent traces priority to a series of applications, including: (1) U.S. Application No. 372,692 filed on January 13, 1995; (2) U.S. Application No. 959,856 filed on November 12, 1992 (the "'856 application"), (3) U.S. Application No. 759,106 filed on September 6, 1991; (4) U.S. Application No. 215,602 filed on July 1, 1988; (5) U.S. Application No. 910,230

filed on February 6, 1986; (4) U.S. Patent Application No. 640,081 filed on August 8, 1984 ("the 1984 U.S. application"); (5) PCT Application PCT/DK83/00118 filed on December 9, 1983 ("the 1983 PCT application"). ('352 patent, col. 1 at ll. 4-16)

23. The '352 patent generally discloses a process to prepare a desired protein. (See '352 patent, col. 1 at ll. 17-19)

24. In particular, the '352 patent describes using an aminopeptidase, preferably DAP I, to cleave a pro-sequence containing an even number of amino acids thereby forming a desired protein. ('352 patent, col. 1 at ll. 56-60)

25. The '352 patent discloses nine examples. Examples 2-4 indicate that DAP I from Boehringer Mannheim was used to cleave the pro-sequence from the desired protein. None of the examples mention using DAP I from Sigma. ('352 patent, col. 4 at ll. 50-col. 5 at ll. 5)

26. The '352 patent includes two independent claims directed to biosynthetic ripe hGH.

27. Claim 1 recites:

> Biosynthetic ripe human growth hormone free of contaminants from pituitary derived human growth hormone.

('352 patent, col. 10 at ll. 7-9)

28. Claim 2 recites:

> Biosynthetic ripe human growth hormone produced by expressing an amino terminal extended human growth hormone fusion protein in a microorganism capable of

such expression, enzymatically cleaving the amino terminal extension and recovering the biosynthetically produced ripe human growth hormone.

('352 patent, col. 10 at 10-15)

29. In May 1997, plaintiffs filed a request for reexamination of the '352 patent based upon a substantial new question of patentability posed by various prior art references including U.S. Patent No. 4,755,465 (the "Gray '465 patent"), U.S. Patent No. 4,775,622 (the "Hitzeman '622 patent"), and U.S. Patent No. 4,745,069 (the "Mayne '069 patent"). (NNX 792 at NNG 0023024; NNG 0023047) Plaintiffs also sought to amend claims 1 and 2 and add new claim 3 as follows:

Claim 1. (Amended) Biosynthetic ripe human growth hormone of **at least 99% purity**, **which is** free of contaminants from pituitary derived human growth hormone.

Claim 2. (Amended) Biosynthetic ripe human growth hormone produced by expressing an amino terminal extended human growth hormone fusion protein, **wherein the amino terminal extension is negatively charged**, in a microorganism capable of such expression, enzymatically cleaving the amino terminal extension and recovering the biosynthetically produced ripe human growth hormone.

Claim 3. Biosynthetic ripe human growth hormone free of contaminants from pituitary derived human growth hormone, said human growth hormone being of sufficient purity to be administrable to humans.

(Id. at NNG 0023051)(bolded text shows proposed amendment to claims 1 and 2)

30. In August 1997, the examiner denied the request for reexamination, concluding that the cited prior art did not

raise any substantial new questions of patentability. The examiner stated:

> The [c]laims of the Dalboge et al. patent, for which reexamination is requested, are directed to ripe human growth hormone (hGH) that is free of pituitary contaminants. The patent defines ripe hGH as having 191 amino acids. . . . Gray et al. do not claim ripe hGH and no interference of claimed subject matter is apparent. . . . [B]ecause Mayne et al. do not cleave the N-terminally extended [growth hormone] with enterokinase and because such cleavage would be expected to remove the N-terminal extension and truncate hGH at amino acid position 172, Mayne et al. do not teach ripe [growth hormone] . . . Hitzeman et al. did not sequence the entire hGH that was secreted from yeast but sequenced only the N-terminal of secreted hGH. The immunoassay used to detect the secreted hGH would not be expected to differentiate between hGH truncated at the C-terminal by yeast proteases and ripe hGH . . . and therefore this argument is sufficient to void Hitzeman et al. as raising a substantial new question of patentability.

(Id. at NNG 0023105)

E. BTG's '248 Application

31. The '248 application was filed on February 13, 1998. (DE 1002 at 1)

32. The '248 application claims priority to U.S. Application No. 641,488 (the "'488 application") filed on August 16, 1984. (Id.)

33. The '248 application generally discloses a method of removing N-terminal amino acid residues from a eucaryotic polypeptide synthesized in a foreign host using an aminopeptidase enzyme. (Id. at 174)

34. More specifically, the '248 application discloses

using *Aeromonas* aminopeptidase to remove an N-terminal methionine residue and its adjacent leucine residue from a fusion protein for hGH. (Id.)

35. Claim 61 of the '248 application[1] recites:

> Biosynthetic ripe human growth hormone free of contaminants from pituitary derived human growth hormone.

Id. at 168.

36. Claim 62 of the '248 application[2] recites:

> Biosynthetic ripe human growth hormone produced by expressing an amino terminal extended human growth hormone fusion protein in a microorganism capable of such expression, enzymatically cleaving the amino terminal extension and recovering the biosynthetically produced ripe human growth hormone.

Id.

37. Claim 63 of the '248 application recites:

> Bacterially-derived authentic human growth hormone.

Id. at 171.

38. Claim 64 of the '248 application recites:

> Recombinant authentic human growth hormone produced by (a) expressing in a bacterium human growth hormone having a methionine residue followed by a leucine residue added to a the N-terminus of authentic human growth hormone, (b) enzymatically removing the amino terminal methionine and leucine and (c) recovering recombinantly produced authentic human growth hormone.

Id.

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[1]Claim 61 is identical to claim 1 of the '352 patent.

[2]Claim 62 is identical to claim 2 of the '352 patent.

39. On February 13, 1998, BTG filed a request for an interference between the '248 application and the '352 patent pursuant to 37 C.F.R. § 1.607.[3] (DE 1002 at 62)

40. On April 8, 1999, the examiner determined that all claims were allowable, but suspended the *ex parte* prosecution pending a decision regarding BTG's request for an interference. (Id. at 16)

41. On July 7, 2000, the administrative patent judge granted BTG's request for an interference pursuant to 35 U.S.C. § 135(a). (Id. at 97)

F. Novo Patent Filings Prior to the '352 Patent

a. The 1982 Danish Application

42. Danish Application No. 5493/82, entitled "A Process For Preparing Ripe Proteins From Fusion Proteins Synthesized in Pro- or Eukaryotic Cells," was filed on December 10, 1982 ("the 1982 Danish application"). (BTX 3)

43. The 1982 Danish application is directed to a process for preparing ripe proteins by, first, expressing in pro- or eukaryotic cells a DNA segment, which codes for the synthesis of a fusion protein and, then, converting the fusion protein produced from the DNA segment to the ripe protein *in vitro*. (Id. at 7-8)

[3]An interference is an *inter parte* proceeding conducted by the Board to resolve questions of priority of an invention. 35 U.S.C. § 135(a).

44. The 1982 Danish application generally describes four procedures for preparing desired ripe proteins from fusion proteins. (See id. at 8-10) To this end, the 1982 Danish application does not recite any information concerning the reaction conditions, such as pH, time, temperature, or enzyme-to-substrate ratio, to be used for the enzymatic cleavage reactions. The 1982 Danish application merely states: "This cleavage reaction is to be optimized with respect to time and enzyme concentration as, in the case of prolonged incubation, aminopeptidase I can also hydrolyze amino acids of the desired product." (Id. at 9)

45. Similarly, the 1982 Danish application does not specify the identity, length, or sequence of the amino acid pro-sequence. The only guidance provided is that when formyl methionine or methionine is not part of the pro-sequence, the C-terminal amino acid, which is directly bonded to the N-terminal amino acid of the desired protein, must be proline, unless the desired protein itself contains proline as the N-terminal or next-to-the-outermost N-terminal amino acid. (Id. at 10) Besides this information, the 1982 Danish application discloses only that "X is an arbitrary amino acid" when the pro-sequence is X-proline and that "the DNA sequence corresponding to this pro-sequence may be selected from among the large number of naturally occurring sequences or may be synthesized *in vitro* when the structure at the nucleotide and amino acid level is known." (Id.

at 8, 9)

46. Lastly, the 1982 Danish application states "proteases . . . and in particular aminopeptidases" are used to cleave pro-sequences in fusion proteins. (Id. at 8) The 1982 Danish application identifies AP I and LAP as suitable aminopeptidases, but does not disclose a particular supplier of LAP. (Id. at 9, 10)

47. The 1982 Danish application does not contain any examples or experimental data. (Id.)

48. The 1982 Danish application contains eight claims directed to processes for preparing ripe proteins. (Id. at 11-13)

49. Claim 1 recites a process to prepare ripe proteins using recombinant DNA technology. (Id. at 11) Claim 1 does not disclose a particular enzyme to cleave the pro-sequence, but states that the enzyme "stops the cleavage of the amino acids of the pro-sequence one step before proline." (Id.)

50. Claim 7 is dependant upon claim 1 and specifies LAP as the cleavage enzyme. (Id. at 12)

51. Claim 8 is dependent upon claims 1-7 and discloses a process to prepare hGH wherein the pro-sequence is specifically phenyl alanine proline. (Id. at 13)

b. The 1983 PCT Application

52. The 1983 PCT application, entitled "A Process for Preparing Ripe Proteins from Fusion Proteins, Synthesized in Pro-

or Eukaryotic Cells," was filed on December 9, 1983 and claims priority to the 1982 Danish application. (BTX 11)

53. The named inventors include Thorkild Christensen, Per Balschmidt, Hans Henrik Dahl, and Kim Hejnaes. (Id.)

54. The 1983 PCT application mirrors the 1982 Danish application, except that the 1983 PCT application includes additional disclosure about the amino acid sequence of the fusion protein and five examples that were not part of the 1982 Danish application. (Id. at 6-7, 9-14) The 1983 PCT application also prefers LAP as the aminopeptidase; the 1982 Danish application did not make this preference. (Id. at 6)

55. Example 1 relates to the synthesize of hGH and describes the experimental procedures used to make hGH in the past tense. (Id. at 9) First, Example 1 discloses that the fusion protein having methionine (Met), leucine (Leu), alanine (Ala), valine (Val), and serine (Ser) ("MLAVS") as the pro-sequence was expressed and evaluated to be greater than 98% pure. (Id.) Second, Example 1 indicates that disulfide bridges in the purified fusion protein were reduced and that the resulting disulfide bonds were broken via S-carbamidomethylation as described in a literature reference. Third, Example 1 states that the purified, reduced, and S-carbamidomethylated fusion protein was treated with LAP as described by D.H. Sprekman and A. Light in the presence of urea and aprotinin. (Id. at 11) Example 1 does not identify a supplier of LAP. Finally, Example

1 discloses that reaction mixture was fractionated by ion exchange chromatography and that the isolated hGH was determined to be 98% pure. (Id.)

56. Dr. Henrik Dalboge wrote the first part of Example 1 (i.e., expression of hGH with the MLAVS pro-sequence), and Mr. Thorkild Christensen wrote the second part of Example 1 detailing the cleavage and purification steps. (See D.I. 64 at 745-46) Mr. Christensen admitted at trial that Dr. Dalboge used past tense to describe the expression step because he actually performed this experimentation. Mr. Christensen also admitted that he had not performed the cleavage and purification steps at the time the 1983 PCT application was filed. (See id. at 747)

57. Example 2 relates to the synthesis of human proinsulin in yeast wherein the pro-sequence was, in order, methionine, leucine, valine, alanine, gylcine, and proline. (BTX 11 at 12) Example 2 discloses that LAP was used to cleave the pro-sequence from human proinsulin. (Id.) Example 2, like Example 1, does not identify a supplier of LAP. Example 2 indicates that isolated human proinsulin was "better than 90% pure." (Id. at 12-13)

58. Examples 3-5 relate to the enzymatic cleavage of small peptides with LAP. (Id. at 13-14) Example 3 discloses that the reaction was conducted at a pH of 8.5 and that LAP from Sigma was utilized to cleave the pro-sequence from the small peptide. (Id. at 13) Examples 4-5 do not provide a supplier of

LAP or discuss a specific pH for the cleavage reaction. (Id. at 14)

59. The 1983 PCT application contains four claims. (Id. at 15-16)

60. Claim 1 is directed to a process for preparing ripe proteins by enzymatic cleavage of a fusion protein with an aminopeptidase. (Id. at 15)

61. Claim 2 is dependent upon claim 1 and discloses that LAP is the aminopeptidase. (Id.)

62. Claim 3 is dependent on claims 1 or 2 and specifies that hGH is the desired protein. (Id. at 16)

c. The 1984 U.S. Patent Application

63. The 1984 U.S. application, entitled "Process for Preparing Ripe Proteins from Fusion Proteins, Synthesized in Pro- or Eukaryotic Cells," was filed on August 8, 1984 and claims priority to the 1983 PCT application and the 1982 Danish application. (NNX 322 at 1)

64. The 1984 U.S. application is identical to the 1983 PCT application; it contains the same disclosure and same five examples.[4] (Id. at 16-33)

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[4]At filing, Novo attempted to add a sixth example to the 1983 PCT application describing the production of hGH by cleaving the pro-sequence methionine, phenylalanine, glutamic acid, and glutamic acid ("MFEE") from the fusion protein MFEE-hGH using LAP. (Civ. No. 02-235-SLR; Paper 124 at 9) The cleavage reaction was performed at a pH of 5.0, and acetamide was added to the reaction mixture. (Civ. No. 02-235-SLR; NNX 332 at 39-40) The PTO refused this addition.

65. During the *ex parte* prosecution, Novo abandoned the 1984 U.S. application by failing to respond to the Examiner's letter dated July 8, 1987. (NNX at 81)

G. Novo's Experimentation to Produce hGH

a. After Filing the 1982 Danish application on December 10, 1983 and Before Filing the 1983 PCT Application on December 9, 1983

66. After filing the 1982 Danish application, Novo dedicated a research group, called the "biosynthetic hGH group" or "B-hGH group," to prepare hGH using recombinant DNA techniques. (D.I. 60 at 145)

67. On March 14, 1983, the B-hGH group held their initial meeting at which time they decided to use LAP to synthesis hGH. (Id. at 145-46; BTX 5)

68. On September 12, 1983, the B-hGH group held their fifth meeting. (D.I. 60 at 147-149; BTX 6) The meeting minutes reveal that the group performed "proof of principle work." That is, to test whether the Y-pro stop strategy was a viable way to produce hGH, they made small peptides consisting of the first four amino acids of hGH preceded by an amino acid extension and then attempted to cleave the extension with LAP purchased from Sigma. These experiments were not successful; LAP completely degraded the amino acid extension as well as the first four amino acids of hGH. (D.I. 60. at 148) As a result of this degradation, the group decided to repeat the experiment using LAP purchased from Boehringer. (Id.; BTX 6 at D020672) They also

decided to optimize the cleavage time and amount of enzyme. (Id.)

69. On September 26, 1983, the B-hGH group held their sixth meeting. (BTX 7) The minutes indicate that the group repeated the proof of principle work using slightly longer amino acid extensions and LAP purchased from Boehringer. (D.I. 60 at 150; BTX 7 at D020675) These experiments showed mixed results; correct cleavage occurred, but was accompanied by "inexplicable degradation." (D.I. 60 at 150; BTX 7 at D020675) The group decided to purify the LAP preparation to eliminate any contaminants. (Id. at 150; BTX 7 at D0202675)

70. On October 31, 1893, the B-HGH group held their seventh meeting. (BTX 1313) The minutes state:

> According to Sundin[, Novo's patent attorney,] this application [referring to the 1982 Danish application] is very weak. Especially the application is wanting of good practical examples besides the results with small peptides already present . . . It would be best if we could use the modified B-hGH with the leucin aminopeptidase. This involves culturing and purification of the leucin aminopeptidase (as it perhaps also contains trypsin and chymotrypsin-like proteases).

(Id. at NNDEII 002539) The minutes also state: "JWH/THC have set up a pH-static system to enable easy supervision of the leucin aminopeptidase activity. The enzyme has an activity maximum at pH 8.4 - 8.6." (Id.)

71. In late November or early December 1983, Novo scientists attempted to synthesize hGH by cleaving the pro-sequence MFEE from the fusion protein MFEE-hGH. The experiment

resulted in partial cleavage of one or two amino acid residues from the N-terminus; ripe hGH was not produced. (D.I. 64 at 711-12)

72. When Novo filed the 1983 PCT application on December 10, 1983, the B-hGH group had not successfully prepared hGH with LAP using recombinant DNA technology. (See D.I. 60 at 159; see also D.I. at 790)

b. After Filing the 1983 PCT Application on December 9, 1983 and Before Filing the 1984 U.S. Application on August 8, 1984

73. On January 19, 1984, the B-hGH group held their eighth meeting. (BTX 12) The minutes report that Novo scientists tested three different pro-sequences, namely (1) Met-PHe-Glu-Glu, (2) Met-Leu-Ala-Leu-Glu, and (3) Met-Leu-Ala-Val-Ser, but were not successful in completely cleaving any one of them from the fusion protein.[5] (Id.; D.I. 60 at 163) The group agreed to optimize the incubation conditions for LAP. The group likewise decided to discontinue preparing additional pro-sequences until the activity and the specificity of LAP were better qualified. (Id. at D020683)

74. On February 13, 1984, the B-hGH group held their ninth meeting. (BTX 15) The minutes reflect that the group investigated the incubation conditions for LAP, including

[5]Notably, the pro-sequence, Met-Leu-Ala-Val-Ser, was described in Example 1 of the 1983 PCT application as being cleaved to yield hGH of 98% purity. (See infra, Section II, G)

incubation time/activity, ion strength/activity, and proportionality of the enzyme amount/activity. In light of this investigation, they opted in the spring of 1984 to terminate all experiments involving the digestion of pro-sequences. They decided to embark on a new approach that relied on the *E. coli* bacteria itself to cleave the pro-sequence, thereby eliminating the need for an enzyme to perform the cleavage. (Id. at B020687; D.I. 60 at 165-66)

75. On March 7, 1984, the B-hGH group held their tenth meeting. (BTX 17) The minutes indicate that pro-sequence cleavage with LAP was still not successful. To this end, the scientists reported that LAP lacks specificity under certain conditions and is "somewhat unstable." (Id. at D020692; D.I. 60 at 168-69) The minutes also indicate that Novo expected "to have a good impression whether it is practically possible to degrade presequences[6] with LAP in about 1 month." (BTX 17 at D020692) The minutes further note that Novo's new approach employing bacteria to cleave pro-sequences showed success as the *Pseudomonas* bacteria was able to cleave a pro-sequence from "pre-hGH." (Id.)

76. On March 7, 1984, Novo first synthesized hGH by cleaving the MFEE pro-sequence from the fusion protein MFEE-hGH

[6]The court understands that the term "presequence," as used in the March 7, 1984 B-hGH group meeting minutes, has the same meaning as the term "pro-sequence."

using LAP from Sigma (Freeze-drying Sigma 112F-8151).[7] (D.I. 64 at 726-728; BTX 468A at D025808) Unbeknown to Novo at the time of this experiment, the particular batch of LAP was contaminated with the DAP I. (D.I. 60 at 170) The reaction also was conducted at a pH much lower than that used in previous experiments due to the types and amounts of additives. (Id. at 171-172) In this regard, Novo scientists planned to run the degradation reaction at pH 8.5, the optimal pH of LAP. (D.I. 64 at 799-800, 803; BTX 468A at D025808) Nevertheless, the scientists unintentionally lowered the pH of the reaction mixture to the range optimal for DAP I by adding 158.4 mg of acetamide.[8] (D.I. 60 at 172, 175) The scientists, however, were not aware of this drop in pH. (D.I. 65 at 804)

77. Several months thereafter, Novo initiated a pilot scale production of ripe hGH using LAP from Sigma with

[7]In Example 1 of the 1983 PCT application, the pro-sequence contained five amino acid residues as opposed to the four amino acid residues found in the pro-sequence of the March 7, 1984 experiment.

[8]On March 13, 1984, Novo scientists repeated the cleavage experiments using MFEE-hGH as the fusion protein with LAP from Sigma. The scientists varied the addition of acetamide to determine its effect on the reaction mixture. (See BTX 468A at D025822) In the first experiment, the pH was set in buffer, acetamide was added, and the pH was readjusted to 8.5. (Id.) In the second experiment, the pH was set in buffer and acetamide was added. The pH was not re-set. It measured 4.8. (Id.) In the third experiment, the pH was set at 8.6; no acetamide was added. (Id.)

alanine, glutamic acid ("AE") as the pro-sequence.[9] (D.I. 64 at 738-741; NNX 850)

H. Novo's Identification of DAP I and Patent Filings Directed to the Use of DAP I to Produce hGH

78. On October 18, 1984, the B-hGH group held their twentieth meeting. (BTX 20) The minutes report that

> [i]t has been tried to degrade [methionine, alanine, glutamic acid] MAE-hGH with LAP from various firms. The Sigma preparation is the only functioning, however, Boehringer LAP has shown a very small activity. It has turned out that the active component in Sigma LAP presumably is not LAP but a 'contaminating' substance. Microsomal LAP has no activity. [Methionine, phenylalanine, glutamic acid] MFE-hGH and [methionine, leucine, glutamic acid] MLE-hGH cannot be degraded.

(Id. at D020740)

79. On February 7, 1985, Novo filed a Danish patent application, entitled "An Enzyme or Enzyme Complex Having Proteolytic Activity," directed to a "heretofore unknown proteolytic enzyme or enzyme complex" capable of cleaving a pro-sequence from a fusion protein of hGH and the use of said enzyme or complex to accomplish enzymatic cleavage (the "1985 Danish application").[10] (DE 1005) The 1985 Danish application discloses that the enzyme or enzyme complex does not cleave

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[9]The exact date of the first pilot batch is unclear from the record. While Novo's witness, Mr. Thorkild Christensen, testified that this pilot production occurred in the summer of 1984, the G-hGH meeting minutes report this pilot on March 18, 1985. In any event, it occurred several months after Novo's initial success in producing ripe hGH.

[10]Novo referred to this "unknown" enzyme as "AP-X." (D.I. 65 at 806)

phenylalanine from the N-terminus of hGH and has its maximum enzymatic activity in the pH range of 4.0 to 5.0, preferably 4.2 to 4.6. (Id. at 2) The 1985 Danish application also discloses that the enzyme or enzyme complex may be irreversibly inactive at a pH of 8.4 at 40ºC. (Id. at 3) The 1985 Danish application further discloses that the enzyme or enzyme complex is isolated from a leucine aminopeptidase containing aqueous extract of pork kidneys and with optimum activity at a pH range of 7 to 9. (Id.) The two examples specifically recite using LAP from Sigma (L-1503, lot 14F-8155).

80. On April 17, 1985, the B-hGH group held their twenty-eighth meeting. (BTX 25) The minutes reveal that Novo scientists suspected that AP-X was DAP I. "If our AP-X is the dipeptidyl peptidase I[,] it is commercially available. Various preparations will be bought and tested." (BTX 25 at D020790)

81. On February 6, 1986, Novo filed a PCT application PCT/DK86/00014, entitled "A Process for Producing Human Growth Hormone," directed to the process for producing hGH from amino terminal extended hGH using DAP I (the "1986 PCT application"). (BTX 28) This application claims priority to the 1985 Danish application. (Id.) The 1986 PCT application discloses that the amino acid extension must consist of an even number of amino acids because DAP I cleaves only dipeptidyl units. (Id. at 3) Additionally, the 1986 PCT application discloses five suitable amino terminal extensions. (Id. at 4-5)

82. On October 3, 1986, Novo filed U.S. Patent Application No. 06/910,230, entitled "Process For Producing Human Growth Hormone," directed to a process of producing hGH using DAP I ("the 1986 U.S. application"). This application claims priority to both the 1986 PCT Application and the 1985 Danish application. Over the next several years, Novo filed other U.S. applications describing the use of DAP I to produce ripe hGH. These applications eventually culminated in the '352 patent.

I. Novo's Statements Subsequent to the '352 Patent Concerning LAP

83. On October 11, 1989, during the *ex parte* prosecution of the 1986 U.S. application, the examiner rejected the claims as unpatentable over the Daum '329 patent.[11] (BTX 311 at 3)

84. On April 11, 1990, in a response after final rejection, Novo distinguished the Daum '329 patent from the invention claimed in the 1986 U.S. application. Novo stated:

> Daum mentioned in column 4 that with LAP it is possible to 'split off N-terminal methionine from foreign proteins containing after the direct synthesis the sequence Met-Uvw-Pro, wherein Uvw can be any desired amino acid except for proline.' This shown in example 13 with the peptide Met-Gly-Pro-amide with the result: Gly-Pro-amide. This disclosure is in accordance with the prior art . . . which discloses that LAP is useful

[11]The Daum '329 patent was filed on July 6, 1982 and claims priority to an application filed on May 29, 1980. (BTX 1373) The Daum '329 patent granted on September 24, 1985. Claim 13 discloses the use of LAP to cleave a fusion protein. (Daum '329 patent, col. 9 at ll. 60-62) Claim 15 recites using the process of Claim 13 wherein LAP is E.C. 3.4.11.1.

> for hydrolysis of **small peptides**. Although applicants have tested LAP with bacterially produced hGH, LAP has been shown **not** to be effective. The effectiveness of LAP seems to disappear as soon as peptides greater than about 50 amino acids are involved. In fact, Daum's examples are conspicuous by the relative absence of examples showing the effectiveness of LAP on larger peptides and Daum does not use bacterially produced protein or peptide in its examples.

(BTX 311 at 5)(emphasis in original)

85. On September 12, 1990, during the *ex parte* prosecution of the 1986 U.S. application, Novo filed a declaration on behalf of Jorli Ringsted, John Pedersen, and Thorkild Christensen, all of whom were inventors named on the '352 patent, detailing the ability of LAP to remove a pro-sequence from the fusion protein for hGH ("1990 Declaration"). (BTX 23) In the experiments described, the Novo scientists varied the pH of LAP, the amount of LAP used, the concentration of acetamide added to the cleavage mixture, and the supplier of LAP. In particular, the Novo scientists used LAP from Sigma (L1503, batch 14F-8155) in all examples, except example 5 where LAP from various suppliers was tested. In example 2, the Novo scientists compared the ability of LAP from Sigma to cleave the pro-sequences alanine, glutamic acid ("Ala-Glu") and MFEE from the fusion protein for hGH at select pHs. The Novo scientists found that Ala-Glu-hGH showed 100% conversion after 1-2 hours at pH 5.5, 75% conversion after 1 day at pH 6.5, 10% conversion after 1 day at pH 7.5, and 0% conversion after 1 day at pH 8.5. (Id.) The Novo scientists also found that LAP from Sigma was not

able to cleave 100% of the pro-sequence MFEE from the fusion protein MFEE-hGH at pH 5.5 after 1 day. (Id.) In example 5, the Novo scientists compared seven LAP preparations from suppliers such as Sigma, Boehringer, Merck, Serva, and Worthington at a pH of 5.5. (BTX 22 at D021372; D.I. 65 at 942-944). The scientists concluded:

> It is shown that essentially only LAP-preparations from Sigma contain enzymatic activity able to convert Ala-Glu-hGH to mature hGH. LAP-preparations from Merck, Serva, and Worthington did not contain such enzymatic activity at all. It is thus likely that an enzymatic activity different from LAP-activity is contained in the Sigma preparations and to a certain degree in the Boehringer product which can convert Ala-Glu-hGH to mature hGH.

(BTX 23) In sum, the Novo scientists stated:

> The experiments show clearly that a pure LAP-preparation will not convert amino extended hGH to mature hGH. Only LAP-preparations with relevant impurities will have some effect depending upon the nature and amount of the impurity and of course this can lead to misunderstanding about the effect of LAP.

(Id.)

86. On November 13, 1990, two months after Novo filed the 1990 Declaration in connection with the 1986 U.S. application, Novo filed a preliminary amendment during the prosecution of U.S. Patent Application No. 07/595,783 (the "'783 application"), an application that claims priority to the 1986 U.S. application. Novo stated:

> The Examiner has rejected the claims under 35 U.S.C. [§] 103 as allegedly being obvious from Brewer in view of Daum. By Declaration filed September 12, 1990, [a]pplicant showed that a pure LAP-preparation will not convert amino extended hGH to mature hGH, thereby

> supporting [a]pplicant's argument that Daum would not be effective to solve the problem solved by the claimed invention. In an [a]dvisory [a]ction dated September 18, 1990, the [e]xaminer erroneously stated that the [1990] [D]eclaration shows that commercial grade LAP as taught by Daum would have worked. In fact, the [1990] Declaration supports the proposition that it is not LAP, but another enzyme (apparently DAP I), which is responsible for the effectiveness of the Sigma product tested in the [1990] Declaration. The [1990] Declaration clearly shows that commercial grade LAP would not have worked. The only exception is a specific LAP product delivered by Sigma (and not shown to have been investigated by Daum) which contains another enzyme.

(BTX 246 at NNG 0024930)

87. On February 4, 1991 and March 27, 1991, the PTO issued office actions rejecting the claims of the '783 application over the published version of the 1983 PCT application.[12] (BTX 246 at NNG 0024935-36) On September 27,

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[12]In the February 4, 1991 office action, the examiner specifically stated:

> The rejection of claims 1-6 and of new claims 7 and 8 under 35 U.S.C. [§] 103 as unpatentable over Brewer in view of Daum et. al. is maintained . . . Note that the [1990 Declaration] and the remarks in the preliminary amendment filed 13 November 1990 has [sic] been considered but is [sic] not persuasive. It is pointed out that the [1990] Declaration and the remarks in the preliminary amendment clearly show by applicants' own results that a commercial preparation used without further purification would have contained the requisite enzymatic functionality as the commercial grade of LAP contains more than just LAP. . . . Claims 1-6 are rejected under 35 U.S.C. [§] 103 as unpatentable over the combination of the [1983 PCT application] and Daum et. al., and Callahan (Enzymes). The [1983 PCT application] disclose[s] using an aminopeptidase to cleave N-terminal residues from a polypeptide produced from *E. coli* containing and expressing heterologous DNA encoding human growth hormone . . . One of ordinary skill in the art would have been motivated to use any other aminopeptidase as well as the preferred leucine

1991, Novo argued in an amendment in response to the office actions that the 1983 PCT application was "inoperative" and was "clearly not enabling." (Id. at NNG 0024960) Novo stated:

> As shown by the [1990] Declaration filed September 12, 1990, a pure LAP-preparation will not convert amino extended hGH to mature hGH. The [1983 PCT application] is thus inoperative. The [e]xaminer has erroneously maintained that the [1990] Declaration shows that commercial grade LAP would have worked. In fact, the declaration supports the proposition that it is not LAP, but another enzyme (apparently DAP I), which is responsible for the effectiveness of the Sigma product tested in the [1990] Declaration. The [1990] Declaration clearly shows that LAP would **not** have worked. The only exception is the specific "LAP" product delivered by Sigma which contains another enzyme. Certainly those of skill in the art cannot be said to be enabled to practice the invention disclosed in [the 1983 PCT application] if such enablement is dependent on the chance that they purchase "LAP" from a specific supplier. Accordingly, [the 1983 PCT application] is clearly not enabling.

(Id.)(emphasis in original) Novo also asserted that the 1983 PCT application did not provide enough information about aminopeptidase enzymes, despite using the "suitable aminopeptidase" language, to guide one of ordinary skill in the

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> aminopeptidase . . . since using a "suitable amino peptidase" is suggested . . . it is pointed out that the [1990] Declaration and the remarks in the preliminary amendment clearly show by applicants own results that a commercial preparation used without further purification would have contained the requisite enzymatic functionality as the commercial grade of LAP contains more than just LAP and would apparently have cleaved the polypeptide. The remarks with regard to the purity of LAP or of DAP I are not convincing in light of the claims which define the metes and bounds of the invention.

(Id. at NNG 0024934-0024935)

art to DAP I. In this regard, Novo stated:

> The [1983 PCT application] relates specifically to the use of LAP to cleave N-terminal residues from a polypeptide produced in *E. coli*. The [e]xaminer maintains that [the 1983 PCT application] would have motivated the use of other aminopeptidases because it uses the language "a suitable aminopeptidase." However, this language is not sufficient to suggest that DAP I by itself would be effective in the [1983 PCT application] process.

(Id.)

88. Novo stated in the published European Patent No. 0217814, the European equivalent of the '352 patent, that:

> In [the 1983 PCT application], a process for producing i.a. authentic hGH is suggested, wherein a biosynthetically formed N-terminal extended hGH is digested with an aminopeptidase, preferably leucine aminopeptidase (LAP) in order to cleave the extension. The extension consisted of arbitrarily selected amino acids which were removed by stepwise cleavage. However, this process did not work in practice with pure LAP.

(DE 2016 at 3)

J. Novo's Statements During the European Opposition Filed by Eli Lilly and Company Involving LAP

89. In opposing European Patent No. 0217814, Eli Lilly and Company argued that the claims in the European Patent No. 0217814 were invalid on obviousness grounds in view of the 1983 PCT application and two other prior art references. (See BTX 36)

90. On December 5, 1991, Novo refuted this allegation by arguing that LAP, as disclosed in the 1983 PCT application, was inoperable. Novo stated:

> This prompted [Novo] to undertake a fractionation on the LAP from Sigma and it was verified that two different enzymatic activities were present, viz an activity converting Ala-Glu-hGH to hGH and an activity converting Leu-NH2 to Leu and NH3, the true LAP activity. Initially, the inventors believed that a new enzyme had been discovered, but further investigations of the "impurity" verified that the enzymatic activity was in fact DAP I. The presence of DAP I as an impurity in LAP had not been reported earlier. . . . The reason for the inoperability of LAP has not been found. Without wishing to be bound by any particular hypothesis, it could be assumed that due to the size of the hGH molecule and its tertiary structure the extension is oriented in a way that does not make it available to the digestion of the enzyme. Whatever the reason might be, the person skilled in the art might reasonably expect it to be a general limitation vs. aminopeptidases.[13]

(Id. at NNG0025824-002525)

91. Novo also implied that a person of ordinary skill in the art attempting to cleave the pro-sequence from ripe hGH would be prejudiced by the disclosure concerning LAP found in the 1983 PCT application. Novo stated:

> A number of further characterizations were introduced in order to arrive at the invention as claimed in EP-B1-217814, characteristics which could not be adopted by a person skilled in the art from the very general teachings of [the 1983 PCT application] who also first had to overcome the prejudice created by the inefficiency of LAP.

(Id. at NNG0025825)

92. In summarizing its position regarding the inoperability of the process disclosed in the 1983 PCT application, Novo stated:

> [A]n attempt to reproduce [the 1983 PCT application]

[13]Novo offered this same argument to the Canadian Patent Office during the prosecution of the Canadian Patent Application No. 520,332. (See BTX 69 at 4)

> would also establish prejudice against the use of aminopeptidases for digestion of N-temrinal hGH extensions.

(Id. at NNG0025835)

93. Novo ultimately added the following statement about the 1983 PCT application to European Patent No. 0217814 to convince the European Patent Office that its claims were valid in light of the 1983 PCT application:

> In [the 1983 PCT application] a process for producing i.a. authentic hGH is suggested, wherein a biosynthetically formed N-t an aminopeptidase, preferably leucine aminopeptidase (LAP) in order to cleave the extension. The extension consisted of arbitrarily selected amino acids which were removed by stepwise cleavage. However, this process did not work in practice with pure LAP.

(BE 2016, page 3, ll. 33-36)

K. Novo Statements During U.S. Litigation Regarding LAP

94. In 1995, at a hearing in the Southern District of New York, Dr. Henrik Dalboge, one of the named inventors on the '352 patent, testified about Novo's efforts to produce ripe hGH. He particularly explained Novo's experimentation with the LAP enzyme.

> Q: Could you explain to us how the strategy at Nordisk Gentofte to produce authentic human growth hormone of 191 amino acids evolved?
> A: Yes. The strategy was to make use of an enzyme which is called leucine aminopeptidase. This is an enzyme which can say kind of, I don't know if you are familiar with PacMan, is able to remove from the end terminals of protein, one amino acid at a time and this process will stop when the bond to be cleaved encounters the amino acid proline. And since proline is the second amino acid in growth hormone, this enzymatic reaction should stop just at the very beginning of human growth

hormone, giving rise to the mature product of 191 amino acids.

Q: Did that strategy, using leucine aminopeptidase, work?

A: Well, I would say that it was very hard to get this to work at all. We made several different amino terminal extended products, and tried to convert these products into mature human growth hormone, but without success. So we also -- I'm sorry.

Q: What did you do then?

A: We also tried to make some small synthetic peptides that had the same extension or the same sequence as we had in some of our extended products and, in addition to that, a few other amino acids, and we saw that on these synthetic peptides the enzyme did work, but we couldn't get it to work on the extended growth hormone molecules. I don't know how many times I have been standing there when we did the analysis to see whether there were any indication of conversion going on, but we never really saw anything.

(D.I. 62 at 634-35)

L. BTG's Statements About LAP

95. During the prosecution of U.S. Patent Application No.08/400,544, filed March 8, 1995 and entitled "Method of Removing N-Terminal Amino Acid Residues from Eucaryotic Polypeptide Analogs and Polypeptides Produced Thereby," BTG submitted a declaration prepared by Dr. Elhanan Ezra (the "Ezra Declaration"). Dr. Ezra compared the ability of LAP from Sigma with the ability *of Aeromonas* aminopeptidase to cleave the methionine amino acid pro-sequence from the fusion protein Met-hGH. (NNX 270) The results in Table 2 indicate that Sigma LAP released 16.6% of the Met from Met-hGH when a 1:10 enzyme:substrate ratio was used under a pH of 8.5. (Id.,

Appendix B at 5) Dr. Ezra recognized: "[B]oth aminopeptidases were active, but differed greatly in their specificity for substrate and in their optimal assay conditions." (Id., Appendix B at 4) Dr. Ezra concluded that "[t]he experiments unequivocally demonstrate that *Aeromonas* aminopeptidase is significantly and unexpectedly much more efficient than the leucine aminopeptidase enzyme used by [the 1983 PCT Application] and Daum et al. in removing N-terminal methionyl groups from two different polypeptides."[14] (Id. at ¶7)

96. Dr. Ezra testified at trial that he did not review the raw chromatographic data that led to the results presented in the Ezra Declaration prior to filing this document. (D.I. 65 at 1009, 1015) Dr. Ezra instead testified that he reviewed a draft report prepared by a scientist working under his supervision. (Id. at 1009) Dr. Ezra clarified that his assistant looked at the raw data, reconciled the specific retention times shown in the chromatogram, and calculated the specific cleavage efficiencies reported in Table 2 of the Ezra Declaration. (Id.)

97. Dr. Ezra testified that when he reviewed the raw chromatographic data for the first time prior to his deposition, he found the data was inconclusive for several reasons: (1) LAP and the fusion protein both produced a peak very near the

[14]The court notes that the Board did not even consider the Ezra Declaration in its decision. "We also need not and have not considered the Ezra testing . . . in making our decision." (Paper 124 at 36-37)

retention time characteristic for methionine, making it impossible to distinguish the peak for methionine from that due to LAP and/or the fusion protein; (2) the data were below the calibration curve; and (3) the peak allegedly due to methionine was broad and poorly resolved. (Id. at 1008, 1023-24)

M. Statements Regarding Example 1

98. During the *ex parte* prosecution of the '856 application, following an interview with the examiner wherein the examiner requested Novo to point out "where in the priority documents the enablement is present," Novo's in-house patent attorney directed the examiner's attention to several sections of the 1983 PCT application, including Example 1.[15] (See BTX 65 at NNG 0023546-47) Specifically, Ms. Cheryl Agris, Novo's in-house patent attorney, stated:

> Applicants also assert that an enabling disclosure of the invention claimed in the instant application is provided in the priority application. Attached hereto . . . is a copy of [the 1983 PCT application], which corresponds to the [1982 Danish application], filed December 10, 1982. . . . Furthermore, Example 1 . . . of [the 1983 PCT application] is specifically directed to hGH.

(Id.) Later, in a March 17, 1994 office action for this same application, the examiner *sua sponte* raised Example 1 in connection with Novo's priority claims. The examiner observed:

> It appears that the instant invention and that

[15]The court observes that the examiner did not specifically raise the issue of enablement in the office action. (See BTX 65 at NNG 0023528-32). Novo, nevertheless, opted to comment on it in responding to the office action.

> disclosed in the [1983 PCT application] are not the same. Example 1 of [the 1983 PCT application] teaches that the hGH will be extended with Met-Leu-Ala-Val-Ser and this fusion protein expressed in *E. coli*, reduced, alkylated, and exposed to leu-aminopeptidase. These variables are different than those of the instant invention.

(Id.)

99. Novo did not inform its experts, Dr. Kenneth Walsh and Dr. Lydia Villa-Komaroff, that Example 1 contained prophetic data instead of actual experimental results as to the cleavage and purification steps until shortly before the patent infringement action. (D.I. 65 at 932-33) To this end, Dr. Walsh, who focused much of his work on the 1982 Danish application and the 1983 PCT application, was deposed two weeks prior to the start of trial and was unaware that the cleavage steps had not been performed. (D.I. 65 at 932) Dr. Walsh, in fact, testified that he was confident that Example 1 had been performed at his deposition and responded to deposition questions while under this impression. (D.I. 65 at 969-70) Similarly, Dr. Villa-Komaroff testified during her deposition for the interference proceeding that she thought Example 1 represented actual results. (D.I. 62 at 602-604; BTX 343 at 84)

N. The Interference Proceeding

100. On July 7, 2000, the PTO declared a patent interference between the '248 application and the '352 patent and designated the inventors of the '248 application as the "Junior Party" or "Party Blumberg" and the inventors of the '352 patent

as the "Senior Party" or "Party Dalboge." (Paper 1) In the Notice Declaring Interference, the PTO accorded the '352 patent the benefit of priority of the filing date of the 1984 U.S. application (i.e., August 8, 1984). (Id.)

101. The PTO defined a single interference count directed to a composition of matter according to claims 1 or 2 of the '352 patent or claims 61, 62, 63, or 64 of the '248 application.[16] (Id.) Specifically, the count was defined as follows:

> A composition of matter according to claims 61, 62, 63, or 64 of Blumberg (09/023,248)
>
> or
>
> A composition of matter according to claims 1 or 2 of Dalboge (5,633,352).

(Id.)[17]

102. The Party Blumberg initially filed one preliminary motion under 37 C.F.R. § 1.633(g) attacking the benefit of the August 8, 1984 filing date accorded to the Party Dalboge for the

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[16]"A count defines the interfering subject matter between two or more applications or between one or more applications and one or more patents." 37 C.F.R. § 1.601(f). "Each application must contain, or be amended to contain, at least one claim that is patentable over the prior art and corresponds to each count. All claims in the applications which define the same patentable invention as a count shall be designated to correspond to the count." 37 C.F.R. § 1.603.

[17]The parties agree that the count covers hGH in a mixture with "other uncleaved or partially cleaved products." (D.I. 85 at 15) BTG does not agree that the count requires the hGH to be biologically active, as argued by Novo. Nevertheless, BTG has agreed to accept this reading of the count for purposes of the instant appeal. (Id.)

'352 patent.[18] (Paper 24) The Party Blumberg sought a ruling that the '352 Patent is not entitled to the August 8, 1984 filing date because the 1984 U.S. application failed to satisfy the conditions of 35 U.S.C. § 120.[19] More specifically, the Party Blumberg argued that the invention defined by the claims of the '352 patent, which corresponds to the sole count of the interference, was not described in the 1984 U.S. application in sufficient detail to enable one of ordinary skill in the art to make and use the invention as required by 35 U.S.C. § 112, first paragraph.[20] (Id.) In other words, the Party Blumberg argued

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[18]Section 1.633(g) entitles a party to file a "motion to attack the benefit accorded an opponent in the notice declaring the interference of the filing date of an earlier filed application." 37 C.F.R. § 1.633(g).

[19]Under 35 U.S.C. § 120,

> [a]n application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, or as provided by section 363 of this title, which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application.

[20]The nature of the Party Blumberg's preliminary motion is clearly premised on patentability grounds, despite being filed under 37 C.F.R. § 1.633(g). The Party Blumberg should have filed its preliminary motion under either 37 C.F.R. § 1.633(a) or 37 C.F.R. § 1.635. Section 1.633(a) entitles a party to file a "motion for judgment against an opponent's claim designated to correspond to a count on the ground that the claim is not patentable to the opponent." Alternatively, section 1.635

that ripe hGH, the subject matter of the count, could not be produced with the LAP as disclosed in the 1984 U.S. application.

103. The Party Dalboge filed seventeen preliminary motions. (Papers 27-43) For preliminary motion 3, the Party Dalboge requested that the PTO accord it the benefit of the filing dates of the 1983 PCT application filed on December 9, 1983 and the 1982 Danish application filed on December 10, 1982 pursuant to 37 C.F.R. § 1.633(f) and § 1.637(a), (d).[21] (Paper 29) The Party Dalboge's remaining preliminary motions generally concerned the patentability of the claims of the '488 application and were filed pursuant to 37 C.F.R. § 1.633(a).

104. After the Party Dalboge's filing, the Party Blumberg filed three additional preliminary motions. In preliminary motion 2, the Party Blumberg sought to amend claims 61 and 62 and to add new claims to the '248 application pursuant

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entitles a party to file a miscellaneous motion for an order "relating to any matter other than a matter which may be raised under [37 C.F.R. §] 1.633 or [37 C.F.R. §] 1.634." Nonetheless, because (1) the court considers the Party Blumberg's mistake to be one of procedure rather than substance; (2) the Party Blumberg raised the substance of its motion concerning enablement during the interference proceeding; and (3) the Board decided the question of enablement, the court shall address the Party Blumberg's argument concerning whether the invention defined by the claims of the '352 patent was described in the 1984 U.S. application in sufficient detail to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph.

[21]Section 1.633(f)entitles a party to file a "motion to be accorded the benefit of the filing date of an earlier filed application."

to 37 C.F.R. § 1.633(c)(2).[22] (Paper 48) In preliminary motion 3, the Party Blumberg moved to substitute a new count pursuant to 37 C.F.R. § 1.633(c)(1).[23] (Paper 49) Lastly, in preliminary motion 4, the Party Blumberg sought to obtain the benefit of priority for the proposed substitute count pursuant to 37 C.F.R. § 1.633(f). (Paper 50)

105. On March 12, 2002, the Board denied the Party Blumberg's preliminary motion 1 and granted in part and dismissed in part the Party Dalboge's preliminary motion 3. (Paper 124) The Board also dismissed the Party Blumberg's preliminary motions 2-4 and the Party Dalboge's preliminary motions 1, 2, and 4-17 as moot. (Id. at 37) The Board also corrected the priority date for the '352 patent from the filing date of the 1984 U.S. application, as accorded in the Notice Declaring Interference, to the filing date of the 1983 PCT application (December 9, 1983), noting that the two applications were substantially the same. (Id. at 1) The Board awarded priority of invention for the subject matter of the count to the Party Dalboge and entered judgment against the Party Blumberg. (Id.) The Board declined to decide whether the Party Dalboge was entitled to the benefit

[22]Section 1.633(c)(2) entitles a party to file a motion to amend an application claim corresponding to a count or to add a claim to the moving party's application to be designated to correspond to a count.

[23]Section 1.633(c)(1) entitles a party to file a motion to redefine the interfering subject matter by adding or substituting a count.

of the 1982 Danish application because the filing date of the 1983 PCT Application preceded the filing date of the '488 application. (Id. at 36)

106. In denying the Party Dalboge's preliminary motion 1, the Board found that the Party Blumberg premised its Rule 1.633(g) challenge on the wrong standard (i.e., patentability as opposed to priority). (Id. at 20) The Board explained the nature of a priority challenge, recognizing that (1) priority benefit is not the same as the benefit accorded under 35 U.S.C. § 120; and (2) priority benefit establishes a date for a party's constructive reduction to practice of all elements of the count. The Board concluded that the Party Blumberg did "not address whether the 1984 U.S. application describes an enabled embodiment within the scope of the count" to show constructive reduction to practice. For this reason, the Board ruled that the Party Blumberg failed to meet its burden of proof for preliminary motion 1. (Id. at 20-21)

107. Nevertheless, the Board stated that,

> even if the standard [the Party] Blumberg used in evaluating whether [the Party] Dalboge is entitled to the benefit of the filing date of the [1984 U.S.] application was correct, . . . [the Party] Blumberg has not shown **the subject matter of the count** (and not the method of making that subject matter) was described differently in the prior [Party] Dalboge applications. Moreover, [the Party] Blumberg has not sufficiently explained why the description of a single enabled embodiment of ripe hGH produced by **any** method is insufficient for priority benefit since the enablement requirement is met if the description enables any mode of making the invention.

(Id. at 21)(emphasis in original)

108. In reaching this conclusion, the Board observed that the Party Dalboge made inconsistent statements on the issue of whether the 1983 PCT application enabled the production of ripe hGH during the *ex parte* prosecution of applications filed after the '352 patent. The Board, however, concluded that it was not bound by those statements. Rather, the Board afforded greater weight to the objective data found in the 1990 Declaration and less weight to the Party Dalboge's inconsistent statements. The Board reasoned as follows:

> We note that the examiner of the [1984 U.S. application] found the [1990] [D]eclaration 'unconvincing' to show the [1983 PCT Application] was inoperative. Like the examiner, we read the [1990] [D]eclaration as purporting to show that commercial grade LAP would have worked to produce hGH in the method tested. According to the declaration, three commercial grades of LAP out of seven had the enzymatic activity to produce ripe hGH. In particular, the declaration purports to show that two LAP preparations from Sigma and "to a certain degree" one LAP preparation from Boehringer contained enzymatic activity sufficient to convert Ala-Glu-hGH to ripe hGH. [The Party] Blumberg has not satisfactorily shown that selection of a working LAP preparation within those that are purported to have been commercially available at the time of the [1990] [D]eclaration would have required undue experimentation.

(Id. at 24-25)(internal citations omitted)

109. Additionally, the Board distinguished the facts at bar from Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1362 (Fed. Cir. 2003), a case cited by the Party Blumberg to support its argument of non-enablement. The Board found that the 1983 PCT application and the 1984 U.S. application, unlike the patent

implicated in the Genentech suit, were not deficient in describing how to make hGH. To this end, the Board stated:

> Both of the applications specify, for example, the use of a fusion protein where proline is next to the outermost [N]-terminal amino acid . . . and treatment with LAP as the cleavage enzyme. The [1983 PCT application and the 1984 U.S. application] disclose that the LAP used will cleave the pro-sequence but will stop after having hydolyzed the bond just before the dipeptide X-Pro.

(Id. at 36)

III. CONCLUSIONS OF LAW

A. Standard of Review

1. Pursuant to 35 U.S.C. § 146, "[a]ny party to an interference dissatisfied with the decision of the Board of Patent Appeals and Interferences on the interference, may have remedy by civil action."

2. "In such suits the record in the Patent and Trademark Office shall be admitted on motion of either party . . . without prejudice to the right of the parties to take further testimony. The testimony and exhibits of the record in the Patent and Trademark Office when admitted shall have the same effect as if originally taken and produced in the suit." 35 U.S.C. § 146.

3. The parties before the district court are not limited, however, to the evidentiary record before the Board. New evidence may be admitted concerning issues which were raised by the parties or by the Board itself during the interference

proceeding. See Case v. CPC Int'l, Inc., 730 F.2d 745, 752 (Fed. Cir. 1984)(finding that Section 146 "authorizes the district court to accept all proffered testimony on issues raised by the parties during the proceedings below or by the [B]oard's decision").

4. "Because the record before the district court may include the evidence before the Board as well as evidence that was not before the Board, we have often described the district court proceeding as 'a hybrid of an appeal and a trial de novo.'" Winner Int'l Royalty Corp. v. Ching-Rong Wang, 202 F.3d 1340, 1345 (Fed. Cir. 2000)(citations omitted).

5. The Federal Circuit has held "that the admission of live testimony on all matters before the Board in a section 146 action . . . makes a factfinder of the district court and requires a de novo trial." Id. at 1347. Live testimony in this context includes testimony that may be identical or similar to testimony that was offered to the Board in the form of affidavits or deposition transcripts. Id.

6. In explaining its reasoning, the Federal Circuit observed that

> [o]ur holding comports with the notion that 'the credibility of the witnesses and the weight to be given to their testimony and the other evidence in the record . . . is a matter for the trier of facts.' Further, our holding also establishes a clear rule that live testimony admitted on all matters that were before the Board triggers a de novo trial. If our holding were otherwise it might be difficult to administer.

Id. at 1347-48.

7. In the case at bar, the parties admitted live testimony from various witnesses, some of whom also submitted testimony to the Board in the form of declarations during the interference proceeding. This court, therefore, shall review the Board's decision both as to the facts and the law de novo.

B. Priority of Invention

8. BTG must prove that the 1983 PCT application does not enable production of biologically active ripe hGH to prevail in the instant § 146 action.[24] See 37 C.F.R. § 1.637(g). "A patentee cannot obtain the benefit of the filing date of an earlier application where the claims in issue could not have been made in the earlier application." Mendenhall v. Cedarapids Inc., 5 F.3d 1557, 1566 (Fed. Cir. 1993). Put differently, "[i]t is elementary patent law that a patent application is entitled to the benefit of the filing date of an earlier filed application only if the disclosure of the earlier application provides support for the claims of the later application, as required by 35 U.S.C. § 112." In re Chu, 66 F.3d 292, 297 (Fed. Cir. 1995).

C. The Legal Standard for Enablement

9. The statutory basis for the enablement requirement

[24]Recall that the Board admitted to having erred in assigning the benefit of priority of the filing date of the 1984 U.S. application instead of the filing date of the 1983 PCT application to the '352 patent. (See *infra*, Section II, N) The priority date in dispute, therefore, is the filing date of the 1983 PCT application.

is found in 35 U.S.C. § 112, paragraph 1, which provides in relevant part:

> The specification shall contain a written description of the invention and of the manner and process of making and using it, in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.

10. The Federal Circuit has explained that "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. . . . Tossing out the mere germ of an idea does not constitute enabling disclosure." Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366 (Fed. Cir. 1997).

11. To satisfy the enablement requirement, a specification must teach those skilled in the art how to make and to use the full scope of the claimed invention without undue experimentation. Genentech, 108 F.3d at 1365. "While every aspect of a generic claim certainly need not have been carried out by the inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id. at 1366. The specification need not teach what is well known in the art. Hybritech v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986).

12. Enablement is determined as of the filing date of the patent application. In re Brana, 51 F.3d, 1560, 1567 n. 19 (Fed. Cir. 1995).

13. The use of prophetic examples does not automatically make a patent non-enabling. The burden is on one challenging validity to show by clear and convincing evidence that the prophetic examples together with the other parts of the specification are not enabling. Atlas Powder Co. v. E. I. Du Pont de Nemours & Co., 750 F.2d 1569, 1577 (Fed. Cir. 1984).

14. Some experimentation may be necessary in order to practice a claimed invention; the amount of experimentation, however, "must not be unduly extensive." Id. at 1576.

15. As summarized by the Board:

> The test for whether undue experimentation would have been required is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

PPG Indus. Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564 (Fed. Cir. 1996)(quoting Ex parte Jackson, 217 U.S.P.Q. 804, 807 (1982)).

16. A court may consider several factors in determining whether undue experimentation is required to practice a claimed invention, including: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance disclosed in the patent; (3) the presence or absence of working examples in the patent; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those

in the art; (6) the predictability of the art; and (7) the breadth of the claims. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors are sometimes referred to as the "Wands factors." A court need not consider every one of the Wands factors in its analysis. Rather, a court is only required to consider those factors relevant to the facts of the case. See Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927 F.2d 1200, 1213 (Fed. Cir. 1991).

17. The enablement requirement is a question of law based on underlying factual inquiries. Wands, 858 F.2d at 737.

D. Person of Ordinary Skill in the Art

18. For purposes of the enablement inquiry, a person of ordinary skill in the art at the time when the 1983 PCT application was filed was someone with a bachelor's degree in a biological science such as biochemistry, enzymology, cell biology, or molecular biology. (D.I. 64 at 873; D.I. 61 at 285) This person also would have four or five years of laboratory experience working with biological macro molecules and would be familiar with basic techniques used in molecular biology. (D.I. 61 at 285-86; D.I. 60 at 136)

E. Enablement of the 1983 PCT Application

19. At the outset, the court recognizes that protein chemistry blossomed in the period from 1960 to 1980 and was an established discipline by the 1980s. (See D.I. 64 at 869) The court observes that recombinant DNA technology, by contrast, was

only in the early stages of development in the early 1980s. BTG's expert, Dr. Andrew C. Webb, testified at trial that

> [t]he whole field of recombinant DNA technology was still very much in its infancy. . . . It was clear that one could do this process of cloning genes, but there were clearly idiosyncracies associated with the particular system and the particular gene clone it was dealing with, which one was not altogether aware of at the time, because there was not a huge amount of information.

(D.I. 61 at 235) Dr. Webb also explained that the experimental techniques were "primitive" and that "it was a time of struggling with a new technology in its infancy." (D.I. 60 at 135) Therefore, because the invention disclosed in the 1983 PCT application involved the combination of a young technology and an established field, the court concludes that the applications in dispute must offer greater guidance to one of skill in the art than if the invention involved an established field alone.

20. Having made this distinction, the court finds that the 1983 PCT application is not enabled because one of ordinary skill in the art would not have been able to produce ripe hGH at the time this application was filed using the disclosed information. The 1983 PCT application does not describe in any workable detail how to synthesize ripe hGH from a fusion protein. It discusses such production only in vague, general terms. In this regard, the 1983 PCT application does not identify the requisite characteristics for the pro-sequence, which potentially could be selected from an infinite number of possibilities given that there are roughly twenty naturally occurring amino acids.

The 1983 specification merely states that the fusion protein has the formula $(Y_m \ldots Y_2\text{-}Y_1)\text{-}(Pro)_p\text{-}(X_1\text{-}X_2 \ldots X_n)$ where $(Y_m \ldots Y_2\text{-}Y_1)\text{-}(Pro)_p$ is the pro-sequence, m is an integer greater than 2, Y is an arbitrary amino acid, P is 0 if X_1 or X_2 is Pro and 1 if X_1 or X_2 is different from Pro. (See BTX 11 at 6)

21. The 1983 PCT application likewise does not identify a supplier for LAP. While Example 3 states that LAP from Sigma was utilized, the court is not convinced that a person of ordinary skill in the art would have purchased LAP from Sigma based on this teaching because Example 3 concerns the enzymatic cleavage of small peptides, not large proteins like hGH. Moreover, when the 1983 PCT Application was filed, there were about a dozen different suppliers of LAP on the market, two of which were as well recognized as Sigma. (See D.I. 61 at 348-49) As well, Sigma was not necessarily a preferred vendor for enzymes. (Id.)

22. Assuming, arguendo, that one of skill in the art would have purchased LAP from Sigma,[25] there is no evidence to show that each and every Sigma LAP preparation available at the time the 1983 PCT application was filed was contaminated with DAP

[25]Novo's experts, Dr. Lydia Villa-Komaroff and Dr. Kenneth Walsh, testified that one of ordinary skill in the art would have naturally turned to Sigma to supply LAP because every lab has a Sigma catalogue and Sigma products were reliable and priced cheaper than products from other suppliers. (See D.I. 61 at 449; D.I. 65 at 995)

I. The evidence shows only that the preparations available in 1984-1985, after the 1983 PCT application was filed, were contaminated with DAP I. Indeed, the Board even acknowledged the lack of evidence concerning the types of LAP preparations available when the 1983 PCT application and the 1984 U.S. application were filed. (See Paper 124 at 25) If a person of ordinary skill in the art happened to purchase an uncontaminated preparation, then such person would not have been able to cleave the pro-sequence from the fusion protein for hGH with any marked degree of success. To this end, Novo tested LAP preparations from Sigma, Boehringer, Merck, Serva, and Worthington at a pH 5.5. The Novo scientists concluded that "[t]he experiments show clearly that a pure LAP preparation will not convert amino extended hGH to mature hGH. Only LAP-preparations with relevant impurities will have some effect depending upon the nature and amount of the impurity." (See BTX 23) Contrary to the Board's interpretation of this data, to wit, "we read the [1990] [D]eclaration as purporting to show that commercial grade LAP would have worked to produce hGH in the method tested," the court accepts the conclusion offered by the Novo scientists who conducted the experiments. Indeed, the data itself shows that only a lyophilized cytosol Sigma L-1503, a suspension cystosol Sigma L-9876, and a suspension cytosol Boehringer 107182 showed 100, 5-10, and 0.1-1 activity per unit, respectively. The remaining "pure" LAP preparations did not show any activity per

unit. (See BTX 23 at NNG 0025118) Additionally, although the Ezra Declaration showed that Sigma LAP was able to hydrolyze 16.6% of the Met pro-sequence from the N-terminus of the Met-hGH fusion protein under a pH of 8.5, Dr. Ezra explained that the raw data supporting the report result of 16.6% were inconclusive.

23. The 1983 PCT Application also fails to indicate that the enzymatic cleavage reaction should be performed at a pH significantly lower than that of the optimal range of 7.5-9.0 for LAP. In fact, none of the examples in the 1983 PCT application specify a pH range for the enzymatic cleavage. Example 1 merely disclosed that the reduced and S-carbamidomethylated fusion protein was treated with leucine aminopeptidase as described by D.H. Sprekman and A. Light. However, as noted by the Board, it is unclear from the language in Example 1 whether the Sprekman and Light references describe how to treat the fusion protein or whether they describe the functionality of the LAP. Furthermore, one of ordinary skill initially would use LAP at pH 8.5, its optimal pH. (See D.I. 61 at 442-43) Since LAP is inoperable and DAP I is inactive at this pH, enzymatic cleavage likely would not occur even using a contaminated LAP preparation purchased from Sigma.

24. Given that the reaction parameters disclosed in the 1983 PCT application were insufficient as discussed above, the court finds that one of skill in the art would have had to engage in undue experimentation in order to produce ripe hGH. In

this regard, the court notes that one of ordinary skill in the art, at minimum, would have had to vary the pro-sequence, aminopeptidase enzyme, pH, temperature, time, and enzyme to substrate ratio. Mindful that the quantity of experimentation does not bear upon whether it is considered unduly extensive, the court, nonetheless, concludes that having to experiment with all of these parameters in order to identify a process to produce ripe hGH would be far from routine.

25. First, one of skill in the art would not vary all of the parameters in the same experiment, but instead would likely proceed in a methodical fashion, changing only one variable per experiment in order to monitor the effects of that variable on the enzymatic cleavage of the pro-sequence from the fusion protein for hGH. While changing the pH from 8.5 to 7.5 is "not a huge effort in one experiment" (see D.I. 61 at 381-383), changing the number of variables involved in the cleavage of a pro-sequence from the fusion protein for hGH is not simple. If one of skill in the art at the time the 1983 PCT application was filed were touched by the same fortune as Novo scientists, then he/she might have identified the magic parameters after only a short period of experimentation. On the other hand, if such person were not as lucky as the Novo scientists, then he/she would have been forced to perform numerous experiments, the precise number of which would be impossible to predict.

26. Next, if one of skill in the art, who started with

the MLAVS as the pro-sequence as set forth in Example 1 of the 1983 PCT application, failed to achieve cleavage with LAP at a pH in its optimal range, then one of ordinary skill in the art would have been left in precarious position of having to start from ground zero to identify all synthesis variables. The 1983 PCT application does not recite enough information to enable one of skill in art to focus the research effort in any way. The court observes that such task is daunting, especially considering that Novo dedicated a research group to the effort and this group worked for at least one year before succeeding to produce ripe hGH. First, considering only the cleavage enzyme, there were about ten aminopeptidases known to recognize the Y-Pro stop signal at the time the 1983 PCT application was filed that could have been used to enzymatically cleave the pro-sequence from the fusion protein for hGH. (See D.I. 885) Next, as previously mentioned, there were an infinite number of possible pro-sequences to use given the sheer number of naturally occurring amino acids. Even if one of ordinary skill in the art appreciated that it would be easier to separate the pro-sequence from the ripe protein by using only charged amino acids and knew which of the naturally occurring amino acids exhibited such charge (see D.I. 64 at 876-77), one of skill in the art still would have to select the number of amino acids to include in the pro-sequence. (See D.I. 64 at 877-882) Finally, altering the number and length of different pro-sequences would require a

significant amount of work. For each desired pro-sequence, one of skill in the art would be required to prepare the DNA for hGH with a different amino acid extension and to transform a colony of bacteria with that DNA. After completing this laborious preparatory work, only then could one of skill in the art test the different extensions in combination with the other variables.

27. In light of both the amount and nature of the experimentation left to one of skill in the art, the court, unlike the Board, finds that the facts at bar are analogous to those in the Genentech decision. Genentech sued Novo for infringement of U.S. Patent No. 5,424,199 (the "'199 patent") directed to a method of producing hGH by expressing hGH with an extension and then cleaving the extension with an enzyme. As a defense to the infringement allegation, Novo argued that the patent in suit was invalid for lack of enablement. Novo asserted that "various combinations of conjugate protein sequences, cleaving enzymes, and reaction conditions needed to be studied to establish a process for producing hGH in useful form." Genentech, 108 F.3d at 1366. The Federal Circuit held that "[w]hen there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required." Id. In reaching this holding, the Federal Circuit observed that

> [t]here is no dispute that the portion of the specification chiefly relied upon by Genentech . . . does not describe in any detail whatsoever how to make hGH using cleavable fusion expression. For example, no

> reaction conditions for the steps needed to produce hGH are provided; no description of any specific cleavable conjugate protein appears. The relevant portion of the specification merely describes three (or perhaps four) applications for which cleavable fusion expression is generally well suited and then names an enzyme that might be used as a cleavage agent (trypsin), along with the sites at which it cleaves ("arg-arg or lys-lys, etc."). Thus, the specification does not describe a specific material to be cleaved or any reaction conditions under which cleavable fusion expression would work.

Id. at 1365.

28. Just as the '199 patent failed to disclose starting materials for the conjugate protein sequences, cleaving enzymes, or reaction conditions necessary to produce hGH, the 1983 PCT application fails to disclose workable starting points to identify a viable pro-sequence, a "suitable aminopeptidase," or other reaction conditions. The Board distinguished the Genentech decision on the grounds that 1983 PCT application disclosed that the desired protein must have proline as the second amino acid and specified LAP as the cleavage enzyme. The court finds these distinction unavailing. The salient points are that: (1) the enzymes disclosed in both the '199 patent and the 1983 PCT application (i.e., trypsin and LAP, respectively) were inoperable; and (2) neither the '199 patent nor the 1983 PCT application provided guidance about the amino acids that should be included in the amino acid extension. Therefore, the court finds the Federal Circuit's holding entirely applicable to the instant suit. The court, consequently, concludes that one of skill in the art would have had to engage in undue

experimentation to produce ripe hGH from a fusion protein.

29. The court substantiates this conclusion by noting that Novo itself was unable to synthesize ripe hGH using the disclosure of the 1983 PCT application. Novo succeeded in producing ripe hGH only after it accidentally altered the cleavage reaction conditions on March, 7, 1984, five months after it filed the 1983 PCT application.[26] That is, it unintentionally used LAP contaminated with DAP I and unintentionally ran the cleavage reaction at a pH lower than 8.5. If Novo scientists had not made these inadvertent changes, or put differently, if fate had not interceded, nothing in the record suggests that Novo would have switched from using what they considered to be "pure" LAP to DAP I or altered the pH to one clearly outside the optimal range for LAP. In fact, Novo itself stated: "The [e]xaminer maintains that [the 1983 PCT application] would have motivated the use of other aminopeptidases because it uses the language 'a suitable aminopeptidase.' However, this language is not sufficient to suggest that DAP I by itself would be effective in the [1983 PCT application] process." Thus, the court finds Novo's own failed attempts at producing ripe hGH pursuant to the teaching of the 1983 PCT application persuasive evidence of non-

[26]Novo misapplies the law of enablement in relying on its success in producing ripe hGH after the 1983 PCT application filing to support the enablement of the 1983 PCT application. (See D.I. 82 at 12) The Federal Circuit has held that evidence of post-filing success is of no significance in deciding the enablement issue. In re Wright, 999 F.2d 1557, 1562-63 (Fed. Cir. 1993).

enablement. Indeed, the Federal Circuit has treated an inventor's failed attempts to practice an invention as evidence of non-enablement on more than one occasion. See AK Steel Corp. v. Sollac, 344 F.3d 1234, 1244-45 (Fed. Cir. 2003)(holding that plaintiff's own failures to make and use the claimed invention at the time of the application supports a finding of nonenablement); see also Genentech, 108 F.3d at 1367 (holding that "[t]he failure of skilled scientists, who were supplied with the teachings that Genentech asserts were sufficient and who were clearly motivated to produce human proteins, indicates that producing hGH via cleavable fusion expression was not then within the skill of the art."); Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1372 (Fed. Cir. 1999)(holding that the district court did not err in relying on an inventor's failed attempts as evidence of nonenablement).

30. As well, unlike the Board who opted to ignore statements made by Novo about the 1983 PCT application, the court finds these statements to be further persuasive evidence that the 1983 PCT application is not enabled. Novo consistently stated on multiple occasions before three different patent offices that the disclosure contained within the 1983 PCT application was "inoperative." For example, Novo averred: "Although applicants have tested LAP with bacterially produced hGH, LAP has been shown not to be effective." (BTX 311 at 5) Novo also stated: "[T]he [1990] Declaration supports the

proposition that it is not LAP, but another enzyme (apparently DAP I), which is responsible for the effectiveness of the Sigma product tested in the [1990] Declaration. The [1990] Declaration clearly shows that commercial grade LAP would not have worked." (BTX 246 at NNG 0024930) Finally, Novo could not have proffered a statement any more certain about the non-enablement of the 1983 PCT application than the following: "Certainly those of skill in the art cannot be said to be enabled to practice the invention disclosed in [the 1983 PCT application] if such enablement is dependent on the chance that they purchase 'LAP' from a specific supplier. Accordingly, [the 1983 PCT application] is clearly not enabling." (Id. at NNG 0024960) In light of these admissions, Novo now cannot attempt to turn the table and argue that the 1983 PCT application is enabling as to the production of ripe hGH.

31. In sum, for the foregoing reasons, the court concludes that BTG has proven with clear and convincing evidence that the 1983 PCT application is not enabling as to the single count of the interference. Accordingly, the court reverses the Board's decision awarding the benefit of priority of invention to Novo for the '352 patent.[27]

F. Issues Not Decided by the Board

[27]Because the disclosure found in the 1982 Danish application is virtually identical to the disclosure found in the 1983 PCT application, albeit without the disclosure concerning the amino acid sequence of the fusion protein and the five examples, the court's decision as to the 1983 PCT Application shall apply with equal force to the 1982 Danish application.

32. BTG seeks to raise two issues in this suit which were not before the Board during the interference proceeding. BTG contends that Novo is not entitled to the benefit of the 1983 PCT application because this application involves a different inventive entity than the '352 patent. BTG also argues that Novo engaged in inequitable conduct during both the *ex parte* prosecution of applications leading to the '352 patent[28] and during the interference proceeding. BTG claims that it was not aware of the alleged facts underlying these two contentions during the interference proceeding and only became aware of relevant information during the discovery associated with the instant § 146 action.

33. Before deciding whether to consider the newly raised issues, it is instructive to review the mechanics of an interference proceeding.

A preliminary statement is a formal document that

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[28]Recall that the applications leading to the '352 patent include: (1) U.S. Application No. 372,692; (2) U.S. Application No. 959,856 (the "'856 application"); (3) U.S. Application No. 759,106; (4) U.S. Application No. 215,602; (5) U.S. Application No. 910,230); and (6) the 1984 U.S. application. During the instant appeal and the patent infringement action, however, the parties only offered into evidence the prosecution histories of the 1984 U.S. application and the '856 application. The court declined to allow the parties to supplement the evidence of record post-trial with the prosecution histories of the remaining applications leading to the '352 patent. (See D.I. 96) In light of this, the court confines its inequitable conduct analysis to Novo's conduct during the prosecution of the 1984 U.S. application and the '856 application. The court declines to speculate about Novo's conduct or its representations in the *ex parte* prosecution of the remaining applications leading to the '352 patent.

> serves several purposes. Initially, it permits the issuance of show cause orders by an examiner-in-chief or the Board when it would be futile to take testimony. It also limits a party's proof on date of invention, and provides notice of the opposing party's case at the close of the motions period in most situations. A preliminary statement may be filed at any time during the period for filing motions. It is filed in a sealed envelope and is usually unavailable to the opposing party until the examiner-in-chief in charge of the interference rules on the preliminary motions and directs that it be opened. . . . If the examiner-in-chief's rulings on the preliminary motions do not terminate the interference, the preliminary statements are served on the opposing party and opened. The examiner-in-chief sets the time for discovery and taking testimony as well as a date for a final hearing before a three-member board. After the final hearing, the Board issues a final decision. A party dissatisfied with the Board's decision may request reconsideration of that decision, or it may seek judicial review by proceeding directly to the United States Court of Appeals for the Federal Circuit for review based on the record before the Board. Alternatively, a party may proceed to a district court for a hybrid appeal/trial de novo proceeding in which the PTO record is admitted on motion of either party, but it may be supplemented by further testimony.

General Instrument Corp. v. Scientific-Atlanta, Inc., 995 F.2d 209, 211-12 (internal citations omitted).

34. As evident from the above, preliminary motions play a critical role in an interference proceeding.

> [T]he preliminary motions which a party files or does not file under § 1.633 can have far reaching consequences for both the outcome of the interference and subsequent *ex parte* prosecution. Consequently, it is imperative during the three-month period between declaration of the interference and the filing of preliminary motions to analyze long-range strategy with respect to . . . priority and patentability issues in the interference.

Id. at 212 (quoting Bruce M. Collins, Current Patent Interference Practice (P-H) § 1.3, at 5 (1989)).

35. In general, the Federal Circuit has held that,

> [i]n order for an issue to be raised adequately in an interference proceeding so that it qualifies for evidentiary review in a section 146 proceeding, more is required than passing reference to the subject during the course of the interference proceeding. For the most part, parties should raise issues in the manner clearly specified in the PTO's interference regulations, that is through preliminary motions, motions to correct inventorship, belated motions delayed for good cause or opposition to these motions. Short of such compliance with the regulations, issues may only be deemed raised for section 146 purposes if the record clearly demonstrates that the issue was undeniably placed before the examiner-in-chief, and one or more parties insisted that the issue be resolved in the process of deciding which of the parties was entitled to priority.

Id. at 214; see also Conservolite, Inc. v. Widmayer, 21 F.3d 1098, 1101 (Fed. Cir. 1994)(holding that a party who failed to file a suitable preliminary motion is precluded from raising the issue both at the Board's final hearing and in an action brought pursuant to § 146).

36. The Federal Circuit has recognized an exception to this holding based on the fact that a district court's review of an interference proceeding is an equitable remedy. General Instrument, 995 F.2d at 214 (citing Standard Oil Co. v. Montedison S.p.A, 540 F.2d 611, 616-17 (3d Cir. 1976)). The Federal Circuit has found that a district court may exercise its discretion and admit testimony on issues even though they were not raised before the Board. General Instrument, 995 F.2d at 214; Conservolite, 21 F.3d at 1102. In doing so, some courts have considered whether: (1) there was suppression, bad faith, or gross negligence on the part of the plaintiff in failing to

raise an issue before the Board; (2) whether the evidence was then reasonably available; and (3) whether the issue was or may be more conveniently and expeditiously raised in another judicial proceeding. Id. Other courts have applied a test of due diligence alone (i.e., whether the failure to identify or procure the evidence was attended by bad faith motives or was done for tactical reasons). Id. (citing Velsicol Chem. Corp. v. Monsanto Co., 579 F.2d 1038, 1046 (7th Cir. 1978)) .

37. In exercising its discretion, the court will consider the issues of inventorship and inequitable conduct in the instant opinion, despite the fact that these two issues were not raised via preliminary motion before the Board. BTG offers evidence allegedly unavailable during the interference proceeding and only uncovered during discovery for the instant § 146 action. In this regard, BTG discovered new evidence concerning Novo's development efforts during the 1982-1986 time period and Novo's statements to foreign patent offices. BTG also uncovered new evidence concerning Example 1 in the 1983 PCT application and the 1984 U.S. application, namely, that it was a paper example and did not represent actual experimental results. In raising these issues in the instant suit as opposed to the interference proceeding, BTG does not appear to act in bad faith.

a. Inventorship

38. Under 35 U.S.C. § 120,

> [a]n application for patent for an invention disclosed

> in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, . . . which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of . . . the first application.

39. In 1984, Congress amended § 120 to replace the phrase "by the same inventor" with the phrase "which is filed by an inventor or inventors named in the previously filed application," as shown above. In re Chu, 66 F.3d 292, 298 (Fed. Cir. 1995)(citing Patent Law Amendments Act of 1984, Pub. L. No. 98-622, Sec. 104(b), § 120, 98 Stat. 3383, 3385). The legislative history of this amendment explains the rationale behind this change.

> Subsection (b) of section 105 amends section 120 of the patent law to provide that an application can obtain the benefit of the filing date of an earlier application when not all inventors named in the joint application are the same as named in the earlier application. This permits greater latitude in filing "divisional" applications. For example, if the previously filed application named inventors A and B as the inventors, a later filed application by either A or B could be filed during the pendency of the previously filed application and claim benefit of the previously filed application.

Id.

40. Given both the express wording of § 120 and the legislative history, it is clear that continuation, divisional, and continuation-in-part applications that satisfy 35 U.S.C. § 112, first paragraph, may be filed and afforded the filing date of the parent application for purposes of priority even though

there is not complete identity of inventorship between the parent and the subsequent applications. Id. In other words, an applicant is entitled to claim the benefit of the filing date of the parent application for the subsequent application to the extent that the parent application discloses the subject matter claimed in the subsequent application and there is one inventor in common between the parent application and the subsequent application. Id.

41. Because the '352 patent was filed after 1984 when Congress amended § 120, the '352 patent is entitled to claim priority to an earlier filed parent application if there is at least one inventor in common to the '352 patent and the earlier filed parent. The '352 patent and the 1984 U.S. application both name Mr. Thorkild Christensen as an inventor. Novo, consequently, is entitled to claim priority to the filing date of the 1984 U.S. application for the subject matter contained in the '352 patent that is disclosed in the 1984 U.S. application.

42. BTG does not dispute Novo's general right to claim priority to an earlier filed parent application, contrary to Novo's characterization of BTG's argument. BTG instead argues that the subject matter of count (i.e., claims 1 and 2 in the context of the '352 patent) is not directed exclusively to the invention of Mr. Christensen, but rather is directed to the joint invention of Mr. Christensen and four other inventors who did not work together at the time the 1984 U.S. application was filed.

To this end, BTG argues that Mr. Thorbin Jessen did not join the hGH group until 1985, thereby making it impossible for the Party Dalboge to have conceived of their joint invention in 1983 or 1984. BTG, therefore, contends that the specific subject matter of the count cannot be disclosed in the 1984 U.S. application.

43. The court is unpersuaded by BTG's argument. BTG fails to recognize that joint inventors need not contribute to each and every aspect of a claimed invention. "Inventors may apply for a patent jointly even though (1) they did not physically work together or at the same time, (2) each did not make the same type or amount of contribution, or (3) each did not make a contribution to the subject matter of every claim of the patent." 35 U.S.C. § 116. BTG has not offered any concrete evidence to distinguish the inventive contributions of the inventors named on the '352 patent; the record merely reflects that all five inventors contributed to the research and development work which resulted in the '352 patent. (See D.I. 64 at 676-78) Thus, the court is unable to verify that claims 1 and 2 of the '352 patent do not recite the joint invention of all inventors named on the '352 patent but only the invention of Mr. Christensen. Put differently, BTG fails to show that Mr. Dalboge, Mr. Pedersen, Mr. Ringsted, and Mr. Jessen, the other inventors named on the '352 patent, did not contribute to claims 1 and 2. The court, therefore, concludes that BTG has not met its burden of proving that the 1984 U.S. application cannot

possibly disclose the joint invention of the Party Dalboge.

b. Inequitable Conduct

44. 1. BTG claims that Novo engaged in inequitable conduct during the prosecution of the '856 application and the 1984 U.S. application and during the interference proceeding in three distinct ways. The first focuses on Novo's conduct with respect to Example 1. To this end, BTG argues that Novo submitted Example 1 as part of the 1984 U.S. application knowing the experimental results represented in Example 1 had not actually been performed. BTG also argues that Novo claimed priority to the 1983 PCT application during the prosecution of the '856 application and the 1984 U.S. application and alleged that the 1983 PCT application enabled the respective inventions in part because of the teaching contained in Example 1. BTG further argues that Novo maintained these priority and enablement claims during the interference proceeding for the '352 patent itself. Second, BTG alleges that Novo misrepresented the content of the 1982 Danish application during the prosecution of the '856 application. Third, BTG alleges that Novo did not provide the PTO with either the 1982 Danish application or an English translation of that application during the prosecution of the '856 application.

i. The Legal Standard

45. Applicants for patents and their legal representatives have a duty of candor, good faith, and honesty in

their dealings with the PTO. Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995); 37 C.F.R. § 1.56(a). This duty is predicated on the fact that "a patent is an exception to the general rule against monopolies and to the right of access to a free and open market." Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co., 324 U.S. 806, 816 (1945). The duty of candor, good faith, and honesty includes the duty to submit truthful information and the duty to disclose to the PTO information known to patent applicants or their attorneys which is material to the examination of a patent application. Elk Corp. of Dallas v. GAF Bldg. Materials Corp., 168 F.3d 28, 30 (Fed. Cir. 1999). A breach of this duty constitutes inequitable conduct. Molins, 48 F.3d at 1178.

46. If it is established that a patent applicant engaged in inequitable conduct with respect to one claim, then the entire patent application is rendered unenforceable. Kingsdown Med. Consultants v. Hollister Inc., 863 F.2d 867, 877 (Fed. Cir. 1988). Additionally, "[a] breach of the duty of candor early in the prosecution may render unenforceable all claims which eventually issue from the same or a related application." Fox Indus., Inc. v. Structural Pres. Sys., Inc., 922 F.2d 801, 803-04 (Fed. Cir. 1991).

47. Inequitable conduct in connection with an application that later issues as a patent also may result in loss of priority in an interference proceeding. Donald S. Chisum,

Chisum on Patents § 19.03[6][a][ii] (2003)(citing Steierman v. Connelly, 197 U.S.P.Q. 288 (Comm'r Pat. 1976)).

48. A finding of inequitable conduct is "an equitable determination" and, therefore, "is committed to the discretion of the trial court." Monon Corp. v. Stoughton Trailers, Inc., 239 F.3d 1253, 1261 (Fed. Cir. 2001).

49. In order to establish unenforceability based on inequitable conduct, a defendant must establish by clear and convincing evidence that: (1) the omitted or false information was material to patentability of the invention; or (2) the applicant had knowledge of the existence and materiality of the information; and (3) the applicant intended to deceive the PTO. Molins, 48 F.3d at 1178.

50. A determination of inequitable conduct entails a two step analysis. First, the court must determine whether the withheld information meets a threshold level of materiality. A reference is considered material if there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent. Allied Colloids, Inc. v. American Cyanamid Co., 64 F.3d 1570, 1578 (Fed. Cir. 1995) (citations omitted); see also 37 C.F.R. 1.56(b)(2)("[I]nformation is material to patentability when it. . . establishes . . . a prima facie case of unpatentability of a claim; or . . . refutes, or is inconsistent with, a position the applicant takes in [o]pposing an argument of

unpatentability relied on by the Office, or [a]sserting an argument of patentability."). A reference, however, does not have to render the claimed invention unpatentable or invalid to be material. See Merck v. Danbury Pharmacal, 873 F.2d 1418 (Fed. Cir. 1989).

51. After determining that the applicant withheld material information, the court must then decide whether the applicant acted with the requisite level of intent to mislead the PTO. See Baxter Int'l, Inc. V. McGaw Inc., 149 F.3d 1321, 1327 (Fed. Cir. 1998). "Intent to deceive cannot be inferred solely from the fact that information was not disclosed; there must be a factual basis for finding a deceptive intent." Hebert v. Lisle Corp., 99 F.3d 1109, 1116 (Fed. Cir. 1996). That is, "the involved conduct, viewed in light of all the evidence, including evidence indicative of good faith, must indicate sufficient culpability to require a finding of intent to deceive." Kingsdown, 863 F.2d at 876. A "smoking gun" is not required in order to establish an intent to deceive. See Merck, 873 F.2d at 1422. An inference of intent, nevertheless, is warranted where a patent applicant knew or should have known that the withheld information would be material to the PTO's consideration of the patent application. Critikon, Inc. v. Becton Dickinson Vascular Access, Inc., 120 F.3d 1253, 1256 (Fed. Cir. 1997).

52. Once materiality and intent to deceive have been established, the trial court must weigh them to determine whether

the balance tips in favor of a conclusion of inequitable conduct. N.V. Akzo v. E.I. DuPont de Nemours, 810 F.2d 1148, 1153 (Fed. Cir. 1988). The showing of intent can be proportionally less when balanced against high materiality. Id. In contrast, the showing of intent must be proportionally greater when balanced against low materiality. Id.

53. Because a patent is presumed valid under 35 U.S.C. § 282, inequitable conduct requires proof by clear and convincing evidence. Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 551 (Fed. Cir. 1990).

ii. Inequitable Conduct During *Ex Parte* Prosecution of the 1984 U.S. Application Based Upon Example 1

54. Considering the materiality element of inequitable conduct, the court acknowledges that compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph, does not turn on whether an example is disclosed in a patent application. United States Patent and Trademark Office, United States Department of Commerce, Manual of Patent Examining Procedure § 2164.02 (hereinafter "MPEP"). However, an example, if present, may teach one of ordinary skill in the art how to make and use the claimed invention. Indeed, "[l]ack of a working example is a factor to be considered, especially in a case involving an unpredicable and undeveloped art." Id. Since claim 3 of the 1984 U.S. application is specifically directed to production of ripe hGH, the very subject matter of Example 1, the

court finds that a reasonable examiner would have considered Example 1 as evidence, at least in part, that the enablement requirement of 35 U.S.C. § 112, first paragraph, was satisfied.

55. After reviewing the prosecution history of the 1984 U.S. application, the court finds no specific mention of either Example 1 or the issue of enablement.[29] (See NNX 332 at 0047-0081) The examiner instead rejected the 1984 U.S. application on other grounds. Nevertheless, "[t]o be material, a misrepresentation need not be relied on by the examiner in deciding to allow the patent. The matter misrepresented need only be within a reasonable examiner's realm of consideration." Merck & Co., Inc. v. Danbury Pharmacal, Inc., 873 F.2d 1418, 1421 (Fed. Cir. 1989). In the case a bar, a reasonable examiner certainly would have wanted to know that the cleavage and purification steps were prophetic. Moreover, the Federal Circuit has held that affirmative misrepresentations by the patentee, in contrast to misleading omissions, are more likely to be regarded as material. Rohm & Haas Co. v. Crystal Chem. Co., 722 F.2d 1556, 1571 (Fed. Cir. 1983). Accordingly, the court concludes that Example 1 was material in deciding the patentability of the 1984 U.S. application.

56. Focusing on the intent element of inequitable conduct, the 1983 edition of the MPEP provides:

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[29]Since Novo abandoned the 1984 U.S. application on July 8, 1987, the prosecution history for this application is not extensive and only involves two office actions and one response.

> Simulated or predicted test results and prophetical examples (paper examples) are permitted in patent applications. . . . Paper examples describe the manner and process of making an embodiment of the invention which has not actually been conducted. **Paper examples should not be represented as work actually done. No results should be represented as actual results unless they have actually been achieved. Paper examples should not be described using the past tense.**

MPEP § 608.1(p)(United States Government Printing Office, 5th Edition, August 1983) (emphasis added).

57. The 1983 edition of the MPEP also states:

> Care should be taken to see that inaccurate statements or inaccurate experiments are not introduced into the specification, either inadvertantly or intentionally. For example, stating that an experiment "was run" or "was conducted" when in fact the experiment was not run or conducted in [sic] a misrepresentation of the facts.

Id. at § 2000.9.

58. The MPEP has no binding force, but serves as an official interpretation of the statues or regulations with which it is not in conflict. See Litton Sys., Inc. v. Whirlpool Corp., 728 F.2d 1423, 1439 (Fed. Cir. 1984), *overruled on other grounds by* Two Pesos, Inc. v. Taco Cabana, Inc., 505 U.S. 763 (1992). The MPEP, therefore, guides patent attorneys and patent examiners on the procedural matters involved in filing and prosecuting patent applications.

59. Example 1 is a paper example because it describes work not actually conducted. It should have been written in present tense pursuant to the guidelines set forth in the MPEP for paper examples. By writing the cleavage and purification steps in the past tense, Novo improperly suggested to a person of

ordinary skill in the art that ripe hGH was produced with 98% purity using the described methodology. The court, however, notes that failure to follow the MPEP does not, in of itself, amount to inequitable conduct. See Nintendo of America Inc. v. Magnavox Co., 707 F. Supp. 717, 730 (S.D.N.Y. 1989). Nevertheless, the court recognizes that the Federal Circuit upheld the district court's finding of inequitable conduct in Hoffmann-La Roche, Inc. v. Promega Corp., 323 F.3d 1354 (Fed. Cir. 2003), where Roche included an example with very specific results written in past tense for experimentation not actually performed. Without more, the court is apt to follow the rationale set forth in Roche and conclude that Novo, like Roche, purposefully sought to mislead the PTO into issuing a patent for the claimed invention.

60. Upon careful consideration of the facts at bar, however, the court finds a key difference between the facts in Roche and those implicated in the instant litigation. Unlike Roche, who provided no reasonable explanation or evidence to explain why the past tense was used to describe an experiment that was not conducted, Novo explained why Mr. Christensen used past tense to describe the cleavage and purification steps. Mr. Christensen testified at trial that he did not consciously use past tense, but instead focused on preparing an example to illustrate enzymatic cleavage and an expected purity for ripe hGH.

Q: Why did you write [the second part of Example 1] in the past tense?
A: Well, I do not remember that we ever thought about what tense we should write it in, so what I - I just wrote it in the past tense.
Q: When you wrote - when you wrote your portion of Example 1 of the 1983 application, did you think it would be possible to remove an amino extension in the manner described in the example?
A: Yes. We thought it would be possible.
Q: In the - at Line 21 of the example, there's a reference to purified fusion protein was evaluated to be more than 98 percent pure.
A: Yes.
Q: Why did you write that?
A: I think 98, that is what we were heading for and, from the experience we had at the company, it was a reasonable purity to obtain.

(Novo Nordisk Pharms. v. Bio-Technology Gen. Corp., Civ. No. 02-332-SLR; D.I. 64 at 748) Based upon this testimony, the court concludes that Mr. Christensen did not intentionally breach his duty of candor and good faith. Rather, the evidence suggests that Mr. Christensen's use of past tense was merely an oversight on his part, likely due to the fact that Mr. Christensen is trained as a scientist, not as a patent attorney familiar with the teachings of the MPEP.

61. Balancing the materiality and intent showings, the court observes that "[a]n equitable judgment must be made that, in light of all the particular circumstances, the conduct of the patentee is so culpable that its patent should not be enforced." LaBounty Mfg. v. United States ITC, 958 F.2d 1066, 1070 (Fed. Cir. 1992). The facts at bar do not show that Novo's conduct during the *ex parte* prosecution of the 1984 U.S. application clearly and convincingly rises to the requisite level of

culpability for a judgment of inequitable conduct. Accordingly, the court concludes that Novo did not engage in inequitable conduct during the *ex parte* prosecution of the 1984 U.S. application.

iii. Inequitable Conduct During *Ex Parte* Prosecution of the '856 Application Based Upon Example 1

62. The prosecution history of the '856 application suggests that the examiner considered Example 1 in determining whether the 1983 PCT application enabled the invention claimed in the '856 application. When requested by the examiner to point out where enablement was present in the 1983 PCT application, Novo specifically directed the examiner's attention to Example 1. Thereafter, in deciding the priority claim, the examiner specifically commented on Example 1. From this evidence, the court concludes that Example 1 was material in deciding whether the 1983 PCT application enabled the invention of the '856 application. Thus, the court finds that the materiality element is satisfied.

63. Turning to consider the intent element, the court finds that Novo, nine years after it first submitted Example 1 to the PTO, knew or should have known that the examiner would have considered the fact that Example 1 contained prophetic data important in evaluating whether the 1984 U.S. application enabled the invention of the '856 application, particularly in light of the fact that Novo never successfully produced ripe hGH using the

methodology described in Example 1. Despite this, Novo did not alert the examiner that the cleavage and purification steps had not been performed or that the purity result was merely a prediction.

64. The facts at bar are analogous to those in Grefco, Inc. v. Kewanee Industries, Inc., 499 F. Supp. 844 (D. Del. 1980), *aff'd without publ. opinion*, 671 F.2d 495 (3d Cir. 1981). In Grefco, the patentee fabricated "test results" to convince the examiner that the claimed invention was superior over the prior art. The patentee also told the examiner that the claimed invention had been successfully tested when it actually had failed twice. The court observed that the examples that contained the fabricated test results were an integral part of the patentee's overall theory of patentability. Id. at 868. The court stated:

> This court and the Third Circuit have . . . been particularly vigilant in requiring patent applicants to disclose all pertinent test results. . . . Grefco does not contend that simply because the test results were learned after the filing of the patent application, they need not be disclosed. Such a rule of law would be contrary to the requirement of high standards of conduct in proceedings before the PTO.

Id. at 867. The court, consequently, held that the patentee's misrepresentation and non-disclosure prevented the examiner from fairly assessing the application against the statutory criteria of utility, anticipation, and obviousness. Id. at 869. At the same time, the court held that it was immaterial whether the misrepresentation and non-disclosure was due to an affirmative

intent to deceive the PTO or simply due to gross negligence on the part of the inventors. Id. at 870. Therefore, the court concluded that the patentee's conduct before the PTO amounted to inequitable conduct.[30] Id.

65. Similar to the patentee in Grefco who presented fabricated test results, Novo directed the examiner's attention to Example 1 to show that the 1983 PCT application enabled the invention claimed in the '856 application, but did not inform the examiner that it failed to produce ripe hGH following the methodology outlined in Example 1 after repeated attempts. Novo's misrepresentation and non-disclosure prevented the examiner from fairly assessing whether the 1983 PCT application enabled the invention of the '856 application. Consequently, the court concludes that Novo's conduct during the prosecution of the '856 application was the product of an affirmative intent to deceive the examiner.

66. BTG has established by clear and convincing evidence that Novo committed inequitable conduct during the prosecution of the '856 application based upon its treatment of Example 1 of the 1983 PCT application. As a consequence of this conduct, the court holds the '352 patent, a downstream

[30]Notably, when considering the Grefco case in the context of another case involving charges of inequitable conduct, the Federal Circuit commented that "[i]ntent and materiality were clearly established in Grefco." Atlas Powder Co. v. E. I. Du Pont de Nemours & Co., 750 F.2d 1569, 1578 (Fed. Cir. 1984).

continuation of the '856 application, unenforceable.

iv. Inequitable Conduct During the Inference Proceeding Based Upon Example 1

67. The court finds that a reasonable board would have considered Example 1 to be material in deciding whether the 1984 U.S. application satisfied the enablement requirement for the subject matter of the interference count. True to form, the Board looked to Example 1 and reviewed expert testimony related to the whether the steps described therein enabled one of ordinary skill in the art to produce ripe hGH. (See Paper 124 at 14-16; 29-33) Additionally, the Board discussed Example 1, albeit not the precise purity results misrepresented by Novo, in the context of whether undue experimentation was required to produce ripe hGH. The Board cautioned that "[t]he entire disclosure may be relied upon for enablement and not merely exemplified material." (Paper 124 at 29-30) Accordingly, the court concludes that the materiality element is satisfied for the interference proceeding.

68. The court also concludes that the intent element is satisfied for the interference proceeding. Novo, sixteen years after it included Example 1 in the 1983 PCT application, did not notify the Board that the cleavage and purification steps described in Example 1 were prophetic. Novo likewise did not inform the Board that it ultimately was unable to produce ripe hGH using the methodology described in Example 1. Novo simply remained silent, thereby allowing the Board to believe that

Example 1 reflected actual experimental results. Such non-disclosure is essentially a representation that what was disclosed is the truth. Moreover, Novo presented extensive expert testimony from Dr. Lydia Villa-Romaroff about Example 1, knowing that Dr. Villa-Romaroff believed that Example 1 represented a working example. The court concludes that Novo knew or should have known that the Board would consider both Example 1 and Dr. Villa Romaroff's expert opinion material to the question of enablement, particularly since this question was the sole focus of the interference.

69. Following the interference proceeding, Novo did not offer any explanation for its silence.[31] Novo merely asserted that it was not required to provide the PTO with a running update of its efforts to make hGH. (See id.) While this contention may be true, Novo was under an affirmative duty to notify the PTO as to the truth of its representations. In this regard, the Supreme Court has observed that "[p]atent applicants are held to a high standard of conduct before the PTO due in part to the Office's inability to verify independently many of the representations made to it." Precision Instrument, 324 U.S. at 818. The court observes that this is especially true when the representations pertain to test results or experiments, because examiners are not equipped to perform their own testing or

[31]In contrast, Novo readily offered an explanation for why it included Example 1 in the 1984 U.S. application.

experimentation. They necessarily rely upon the candor and good faith of applicants in reporting such results.

70. Finding both the materiality and intent showings satisfied, the court concludes, in light of all the circumstances, that Novo engaged in inequitable conduct during the interference proceeding based upon its treatment of Example 1 of the 1983 PCT application. The court is unaware of any specific Federal Circuit precedent that governs the repercussions for engaging in inequitable conduct during an interference proceeding; the majority of cases deal with inequitable conduct in the context of *ex parte* prosecution. Nonetheless, the court concludes that the appropriate sanction in the instant case is to bar Novo from availing the benefit of the filing date of the 1984 U.S. application. The court also find it proper to hold the '352 patent unenforceable, since an interference proceeding forms part of the history associated with a patent.

v. Inequitable Conduct During the *Ex Parte* Prosecution of the '856 Application Based Upon Novo's Representations of the 1982 Danish Application

71. During the *ex parte* prosecution of the '856 application, Novo informed the examiner that the 1982 Danish application "corresponds" to the 1983 PCT application when addressing the question of priority of invention. (See BTX 65 at NNG 0023546-47) BTG argues that this statement misled the examiner into believing that the 1982 Danish application contained the same examples found in the 1983 PCT application

when, in fact, the 1982 Danish application did not include any examples at all. BTG contends that, because of the representation, the examiner decided not to evaluate the 1982 Danish application separately, but instead applied his consideration of the 1983 PCT application to the 1982 Danish application and accorded priority to the filing dates of both the 1983 PCT application and the 1982 Danish application.

72. The court finds that Novo's statement was material to the question of enablement and, in turn, priority of invention. In stating that the 1982 Danish application corresponded to the 1983 PCT application, Ms. Agris implicitly suggested that the examiner need not consider the 1982 Danish application in deciding whether it enabled the subject matter claimed in the '856 application because the 1983 PCT application, in effect, contained the same disclosure. The court finds, however, that a reasonable examiner would have wanted to independently evaluate the 1982 Danish application, especially considering that the disclosure contained in the 1982 Danish application was less than that contained in the 1983 PCT application. The court, therefore, concludes that the materiality element is satisfied.

73. As to the intent element, the court concludes that Novo did not exhibit the requisite deceptive intent. BTG fails to offer any proof as to what meaning Ms. Agris intended to communicate by using the word "correspond." Although Mr. Albert

Jacobs, another Novo patent attorney, testified that he uses the word "correspond" to mean that specifications of the applications are identical and the claimed subject matter is essentially the same (see D.I. 185 at 416-17), the court notes that this term does not connote a universally understood meaning. To this end, the court observes that the word "correspond" has been defined to mean "to be similar, parallel, equivalent, or equal in character." American Heritage Dictionary 327 (2d College Ed. 1982). If Ms. Agris used the word "correspond" intending to communicate "equality" or "equivalence" on the one hand, then it is quite likely that she acted with deceptive intent. On the other hand, if Ms. Agris used the word "correspond" intending to communicate "similarity," then she fairly characterized the relationship between the 1982 Danish application and the 1983 PCT application; indeed, the two applications are similar in that they both relate to the biosynthetic production of proteins and offer the same teaching but for the disclosure directed to the amino acid sequence of the fusion protein and the five examples. Thus, given these conflicting possible scenarios, the court finds that the evidence of record fails to clearly and convincingly establish that Novo intended to deceive the examiner in representing that the 1982 Danish application corresponds to the 1983 PCT application.

74. While the facts at bar establish the materiality element, the court declines to find inequitable conduct. The

degree of materiality does not outweigh the absence of intent. As such, the court concludes that the Novo's conduct was not so culpable as to hold the '352 patent unenforceable on this basis.

vi. Inequitable Conduct During the *Ex Parte* Prosecution of the 1984 U.S. Application Based Upon Novo's Failure to Submit the 1982 Danish Application or Its Translation to the Examiner

75. At the outset, the court finds that evidence of record supports BTG's argument that Novo withheld the 1982 Danish application from the examiner. The prosecution history of the '856 application reveals that Novo claimed priority to the 1982 Danish application upon filing the 1984 U.S. application.[32] (See NNX 322 at 0007) Despite making this claim, it is appears that Novo did not submit a certified copy of the 1982 Danish application, as the box on the new application transmittal form indicating enclosure of the priority document was left blank when other boxes indicating enclosures were checked. Following receipt of this application, the examiner acknowledged Novo's claim for priority in the first office action dated August 15, 1986. (See id. at 0047) Specifically, the office action form states: "Acknowledgment is made of the claim for priority under 35 U.S.C. 119." (Id.) The examiner lined through the number "119" and wrote the number "365" above it, thereby suggesting that Novo's priority claim should have been filed under 35 U.S.C.

[32]Notably, Novo did not indicate the statutory basis for this claim, i.e., whether it sought to avail 35 U.S.C. § 119 or 35 U.S.C. § 365.

§ 365. The court finds this notation important to the inequitable conduct charge at bar. A priority claim under § 119 is different from a priority claim under § 365. Under § 119, an applicant may claim priority to an application previously filed in a foreign country. In contrast, an applicant may claim priority to an earlier-filed international application (i.e., PCT application) designating the United States under § 365. By changing Novo's priority claim from one under § 119 to one under § 365, the court infers that Novo must have submitted a certified copy of the 1983 PCT application instead of the 1982 Danish application. This inference is supported by the fact that the examiner treated the 1984 U.S. application as a continuation-in-part of the 1983 PCT application as opposed to the national phase version of the PCT application.[33] Under the former category, a United States application may claim priority to a PCT application whereas under the latter category, a claim for priority is not

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[33]In this regard, the examiner stated:

> [The 1984 U.S. application] has been filed either as a continuation-in-part of [the 1983 PCT application] filed December 9, 1983 in view of added subject matter present in the amended, published [1983 PCT application] or as an application entering the national phase as regards the original, unamended international application. This application may be properly considered as a continuation-in-part of [the 1983 PCT application] because the United States was noted as a designated state in said [1983] PCT application and because [the 1984 U.S. application] and [the 1983 PCT application] were copending as [the 1984 U.S. application] was filed within twenty months of the December 9, 1983 filed [sic] date of [the 1983 PCT application].

(Id. at 0048)

involved because the PCT application is the same as the United States application. The court further substantiates its inference by noting that the prosecution history of the '856 application contains only a copy of the 1983 PCT application, not a certified copy of the 1982 Danish application. (See id. at 0016-0033)

76. Turning to focus on the elements of inequitable conduct, the court finds the materiality showing satisfied. The 1982 Danish application was critical to Novo's priority claim; a reasonable examiner necessarily would have reviewed it in deciding whether to accord the 1984 U.S. application with priority of invention to the filing date of the 1982 Danish application.

77. The intent element, in contrast, is not satisfied because BTG fails to point to any evidence of record showing that Novo purposefully withheld the 1982 Danish application with the intention of deceiving the examiner.

78. As in the previous situation involving Novo's representations about the 1982 Danish application, the court declines to find inequitable conduct where there is an absence of deceptive intent. Accordingly, the court concludes that Novo's hands were not so unclean as to merit holding its '352 patent unenforceable on this basis.

G. Other Preliminary Motions Dismissed by the Board as Moot

79. Novo argues that if the court reverses the Board's

award of priority to the Party Dalboge, then principles of judicial efficiency mandate that the court address its sixteen preliminary motions presented to the Board and dismissed as moot. Novo asserts that such action would eliminate a later § 146 action. Novo also avers that the court is well situated to adjudicate the mooted motions based on the present record.

80. While the court agrees with Novo that the present record likely is sufficient to decide its mooted motions, the court declines to rule on these motions. The court observes that § 146 is silent as to whether a district court should remand issues presented to the Board but not decided by it. Some district courts in § 146 actions have remanded such outstanding issues. See, e.g., Kochler v. Mustonen, 774 F. Supp 641, 645 (D. D.C. 1991); Plumley v. Mockett, 1999 U.S. Dist. LEXIS 23308 (C.D. Cal. 1999); Goliath Hundertzehnte Vermoegensverwaltungs-Gesellschaft mgH v. Yeda Research & Dev. Co., 68 U.S.P.Q.2d 1703 (D. D.C. 2003). Additionally, this court has proceeded in this very fashion in the past. See Dow Chem. Co. v. Exxon Chem. Patents, Inc., 1998 WL 175883 (D. Del. 1998). On the other hand, other district courts have disfavored remand. See, e.g., Marathon Oil Co v. Firestone Tire & Rubber Co., 205 U.S.P.Q. 520 (N.D. Ohio 1979); Eastman Kodak Co. v. E.I. DuPont de Nemours & Co., 284 F. Supp. 389 (E.D. Tenn. 1968); Monsanto v. Kamp, 269 F. Supp. 818 (D. D.C. 1967); Knutson v. Gallsworthy, 164 F.2d 497, 507 (D.C. Cir. 1947). The court concludes that none of these

latter cases specifically preclude remanding issues that were presented but not decided by the Board.

81. The court notes that the Federal Circuit has not specifically addressed the precise remand issue at bar. The court, nonetheless, finds guidance in Rexam Indus. Corp. v. Eastman Kodak Co., 182 F.3d 1366, 1370 (Fed. Cir. 1999). In this decision, the Federal Circuit has opined that the district court should review the issues of priority and patentability after the Board's full consideration. Id. at 1370. By allowing the Board to make the initial factual and legal findings concerning the mooted motions, the court avails the Board's specialized knowledge of the technology and patent issues in dispute. In addition, the court gives proper deference to administrative agencies, like the PTO, established by Congress. As recognized by the court in Plumley, 1999 U.S. Dist. LEXIS 23308 at *19-20, "remand would be consistent with the modern scheme of administrative law in which specialized agencies are responsible for initial decisions on complex factual and legal matters but are accountable on review to Article III judges." Accordingly, the court remands Novo's mooted preliminary motions to the Board for further consideration consistent with the instant opinion.

IV. CONCLUSION

For the reasons stated, the court overrules the decision of the Board that Novo is entitled to the benefit of priority of the 1983 PCT application on enablement and inequitable conduct

grounds. The court also holds the '352 patent unenforceable due to inequitable conduct. The court further denies Novo's motion to decide its preliminary motions that the Board dismissed as moot; the court remands these motions to the Board for further consideration consistent with the instant opinion. An order shall issue and judgment shall be entered accordingly.

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

BIO-TECHNOLOGY GENERAL CORP.,	)	
Plaintiff,	)	
v.	)	Civ. No. 02-235-SLR
NOVO NORDISK A/S and NOVO NORDISK PHARMACEUTICALS, INC.,	)	
Defendants.	)	

O R D E R

At Wilmington this 3rd day of August, 2004, consistent with the opinion issued this same date;

IT IS ORDERED that:

1) The decision of the Board of Patent Appeals and Interferences of the United States Patent and Trademark Office ("the Board") in Blumberg v. Dalboge, Interference No. 104,422, ("the Interference") is reversed.

2) U.S. Patent No. 5,633,352 is unenforceable due to inequitable conduct.

3) The preliminary motions filed by Novo in the Interference and determined by the Board to be moot are remanded for further consideration consistent with the instant opinion.

Sue L. Robinson
United States District Judge